Final Dossier

Lead

Pb

CAS RN: 7439-92-1
atomic weight = 207.2

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I. Introduction

Lead was nominated by Elizabeth A. Whelan, CDC/NIOSH, from Cincinnati OH on October 4, 2006. Under Reason for nomination, Dr. Whelan supplied the following information:

"The reproductive health effects of lead are fairly well characterized at blood lead levels (BLLs) over 20 µg/dL. At lower levels, there is more debate. A draft document by the Association of Environmental and Occupational Clinics (AEOC) provides medical management guidelines for lead-exposed adults and they state that BLLs of 10-19 µg/dL are associated with "possible spontaneous abortion" and "reduced newborn birth weight. At BLLs below 10 µg/dL, they state "possible adverse population effects suggested by epidemiologic studies." Current occupational exposure limits allow workers (including pregnant women) to have BLLs up to 40 µg/dL. NIOSH is beginning the process to revise its recommended exposure limit (REL) for lead. A CERHR expert panel evaluation of the health effects of lead at lower levels of exposure would help tremendously in this regard. Aside from occupation exposure, other sources of lead for pregnant women include renovation, pica, folk remedies, and lead-glazed ceramics."

On July 25, 2007, the CERHR Core Committee[1] considered this nomination and recommended that CERHR conduct an evaluation of the potential developmental and reproductive toxicity for low-level lead exposure (blood levels < 40 microg/dL). The rationale for conducting a CERHR evaluation is to aid NIOSH in revising the Recommended Exposure Limit (REL) for lead in workers (currently at 40 microg/dL). While a blood lead level of 10 microg/dL is considered elevated in children there are no medical screening guidelines for pregnant women that could be used as the basis for a revised NIOSH REL. The current REL is based on carcinogenicity and not on the more sensitive endpoint of developmental neurotoxicity used by other health agencies. NIOSH is interested in revising the REL to address concerns for reproductive health in workers (i.e., pregnancy outcome, effects in the children of exposed female workers), but use of a developmental/reproductive toxicity endpoint would be a novel health effect for determining a REL. Although the lead literature has been comprehensively reviewed recently in the EPA Air Quality Criteria for Lead (published October 2006), the Core Committee supports the low level lead nomination to CERHR because the unique format and credibility of a CERHR evaluation will be instrumental to NIOSH in revising the lead REL. This is an unusual evaluation for CERHR because the focus of most evaluations is to determine whether a substance is a reproductive and/or developmental toxicant. However, in this case, the starting premise is that lead is a developmental toxicant. The focus of a CERHR evaluation would be to determine a blood level in women and children where concern for reproductive and developmental risks is expressed.

Synonyms for lead include: Blei,C.I. 77575, C.I. Pigment Metal 4, CCRIS 1581, CI 77575, CI pigment metal 4, EINECS 230-100-4, Glover, HSDB 231, KS-4, Lead element, Lead flake, Lead metal, Olow [Polish], Omaha & grant, Pb-S 100, Plumbum, Rough lead bullion, SSO 1.

The main uses of lead are in the manufacture of storage batteries, ammunition, nuclear and x-ray shielding devices, cable covering, ceramic glazes, noise control materials, bearings, brass and bronze, casting metals, solders, pipes, traps, and bends. Lead is used in the material for tank linings, piping, and other equipment handling corrosive gases and liquids. Lead is used in fuel

[1] The Core Committee is an advisory body consisting of scientists from government agencies. Agencies currently represented are: Environmental Protection Agency, Centers for Disease Control and Prevention, Food and Drug Administration, Consumer Product Safety Commission, National Institute for Occupational Safety and Health, and National Institute for Environmental Health Sciences

additives; although leaded fuel is not used in the US for on-road vehicles, fuel containing lead may continue to be sold for off-road uses, including aircraft, racing cars, farm equipment, and marine engines until 2008. Lead may be present in paint pigments, ceramics, plastics, and electronic devices. Lead and lead compounds were used in solder applied to water distribution pipes. According to Air Quality Criteria for Lead, about 60% of the lead used in industry is alloyed with antimony, calcium, tin, copper, tellurium, arsenic, silver, indium, aluminum, sulfur, bismuth, cadmium, or strontium. Lead salts used in industry include acetates, carbonates, halides, silicates, and sulfates. Lead oxides are commonly used in batteries among other applications.

The US Geological Service reported US production of lead at 1.4 billion kg, most of which is used in batteries (Figure 1). According to the Air Quality Criteria for Lead, emissions of lead from natural sources total 19 billion kg/year, largely from wind-borne soil, sea spray, volcanoes, forest fires, and biogenic sources. Emissions from human stationary and mobile sources total 1.6 billion kg annually.

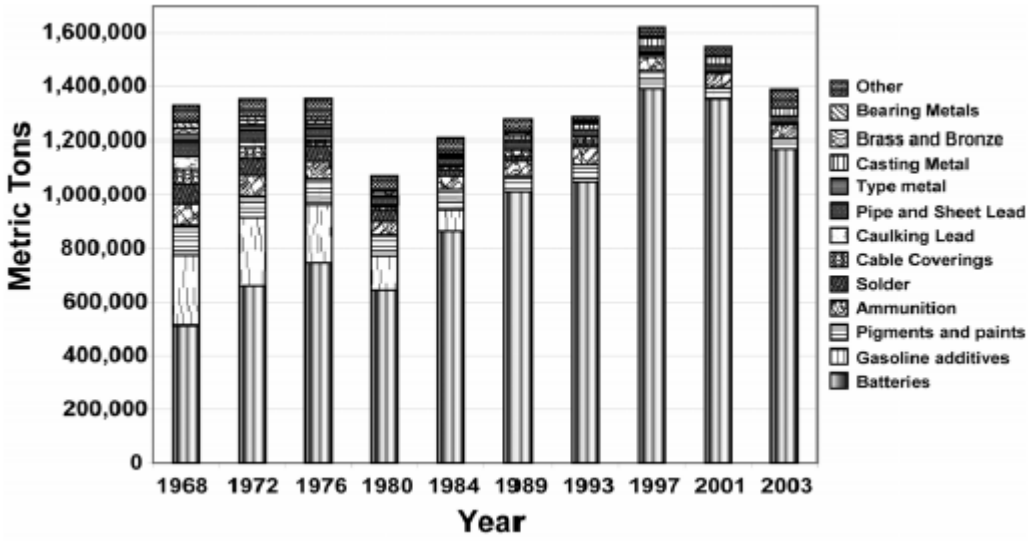

Figure 1. Annual lead production and use in the US
From US Bureau of Mines and USGS, reproduced from EPA Criteria Document

There has long been public concern about lead. Most recently, concern has centered on lead exposure from drinking water, paint, cigarettes, toys, and jewelry. Although removal of lead from motor vehicle fuel has resulted in a decrease in exposure, there has been increased concern about possible adverse health effects, including developmental effects, of low level exposures.

II. Overview

Lead has been the subject of numerous studies and reviews. The most recent IRIS update was in 2004 (http://www.epa.gov/iris/subst/0277.htm). The ATSDR Toxicological Profile on Lead was updated in September, 2005 (http://www.atsdr.cdc.gov/toxprofiles/tp13.pdf). The EPA Air Quality Criteria for Lead was finalized in October 2006 (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=158823#Download). The EPA document is 1261 pages long with additional 996 pages of appendices and constitutes a thorough review of the health literature related to lead. Most of the information in this dossier was obtained from the EPA Air Quality Criteria for Lead.

According to ATSDR (http://www.atsdr.cdc.gov/toxprofiles/tp13-c6.pdf) some of the more important lead exposures have occurred as a result of living in urban environments, particularly in areas near stationary emission sources (e.g., smelters), consumption of produce from family gardens, renovation of homes containing lead-based paint, eating of paint flakes by children, contact with interior lead paint dust, occupational exposure, secondary occupational exposure in families of workers using lead, smoking, and consumption of liquor distilled in lead-soldered equipment. The latest results of the CDC's Adult Blood Lead Epidemiology and Surveillance (ABLES) program indicate that rates of elevated BLLs ranged from 0.06 per 100,000 females of childbearing age at BLLs of ≥40 μg/dL to 10.9 per 100,000 females at BLLs of ≥5 μg/dL. [2] The highest and most prolonged lead exposures are found among workers in the lead smelting, refining, and manufacturing industries. The NIOSH REL and the OSHA PEL (both TWA) are 0.050 mg/m^3.

Blood lead is used as a measure of body lead burden. About 99% of blood lead is located in erythrocytes, and plasma lead (<0.3% of blood lead) may be the toxicologically active fraction. Lead intake and blood lead are better correlated at low than at high lead exposure levels. Most lead in the body (70% in children, 90% in adults) is in bone. Lead can be mobilized from bone during pregnancy, adding to the fraction available for transplacental exposure of the conceptus. In the summaries, below, an indication will be given if blood levels <20 μg/dL were identified in individual studies.

III. Data summaries

The following summaries on developmental and reproductive effects of lead in humans and experimental animals are taken primarily from the EPA Air Quality Criteria for Lead. Additional literature from this document on the neurologic and cognitive effects of lead exposure in humans and literature from experimental animal studies relevant to a CERHR evaluation are summarized in Appendices A – D. New epidemiological and experimental animal studies related to reproduction and development are summarized in Appendices E and F.

A. Developmental

1. Human

Adverse effects of lead on human pregnancy outcome have been reported to be associated with high-level occupational exposures. These reports are somewhat anecdotal and involve lead exposure in cottage industries to levels that were likely to have been well above acceptable contemporary occupational levels. This dossier will focus on possible effects at lower exposure levels.

Lead is believed to cross the placenta freely throughout pregnancy. Measurements at mid-pregnancy and at term show a significant correlation between maternal and fetus blood lead concentrations. (The EPA Air Quality Criteria for Lead summarizes 14 studies on placental transfer of lead in humans).

a. Spontaneous abortion

[2] The rate of being at or above a BLL of 40 μg/dL is similar to or lower in women of childbearing age for occupational exposure. [From: CDC (2007) Lead exposure among females of childbearing age--United States, 2004.MMWR Morb Mortal Wkly Rep. Apr 27;56(16):397-400. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5616a4.htm#tab]

The literature on lead and spontaneous abortion is summarized in Table 1. EPA concluded that there was little evidence to support an association between lead exposure of women and spontaneous abortion.

Table 1. Lead Exposure of Women and Spontaneous Abortion

Reference	Findings
1. Nordström et al., 1978a, 1979	Women working in or living near a smelter had elevated rates of abortion. No measures of lead exposure. Concurrent exposure to arsenic, zinc, and cadmium.
2. McMichael et al., 1986	No relation between blood lead and spontaneous abortion in an Australian smelter town.
3. Murphy et al., 1990	No association between lead exposure and spontaneous abortion in a retrospective cohort study in Yugoslavia (mean blood lead of 17.1 µg/dL in exposed population).
4. Laudanski et al., 1991	No increase in abortion in lead-exposed area of Poland compared to less exposed area.
5. Lindbohm et al., 1991a, Taskinen. 1998	No association between inferred lead exposure (from occupation history) and spontaneous abortion.
6. Tabacova and Balabaeva, 1993	Higher blood lead (7.1 µg/dL) in women with spontaneous abortion than women who carried pregnancy (5.2 µg/dL) in prospective study.
7. Driscoll, 1998	Occupational use of lead-based paint associated with spontaneous abortion (highest OR 4.3, 95% CI 2-9.3). Exposure and outcome ascertained by questionnaire, response rate 59%.
8. Borja-Aburto et al., 1999	Association between blood lead and spontaneous abortion in case-control study in Mexico City, OR 1.8 (95% CI 1.1–3.1) for every 5 µg/dL increase in blood lead.

b. Fetal growth

The literature on lead exposure during pregnancy and fetal growth is summarized in Table 2. The EPA characterized the studies as inconsistent. The studies reporting significant associations were criticized for having not considered confounders and in some cases for not controlling for multiple comparisons. EPA also indicated that use of a short-term measure like blood lead instead of a long-term measure like bone lead could lead to misclassification of lead exposure with a bias toward the null hypothesis.

Table 2. Lead Exposure and Fetal Growth

Reference	Findings
1. Clark, 1977	No association between blood lead and birth weight; cross-sectional study
2. Gershanik et al., 1974	No association between blood lead and birth weight; cross-sectional study
3. Moore et al., 1982	No association between blood lead and birth weight; cross-sectional study
4. Rajegowda et al, 1972	No association between blood lead and birth weight; cross-sectional study
5. Wibberly et al., 1977	No significant correlation between placental lead and birth weight
6. Bogden et al., 1978	No significant difference in maternal or cord blood lead between low birth weight and normal weight babies (means <20 µg/dL)
7. Huel et al., 1981	No difference in maternal or fetal hair lead in small-for-gestational age and normal weight pregnancies
8. Needleman et al., 1984	No association between proportion of births <2500 g and cord blood lead (range <1–35 µg/dL)
9. Bellinger et al., 1991	Reanalysis of Needleman et al., 1984, showing borderline significant associations between blood lead and birth weight <2500 g (RR 1.6, 95% CI 1.0–2.6) and between blood lead and birth weight < 2SD for

	gestational age (RR 1.9, 95% CI 1.0–3.4). Risks increased at blood lead ≥15 µg/dL.
10. McMichael et al., 1986	No relationship between either mid-trimester maternal blood lead or cord blood lead at birth and birth weight. Mean maternal blood lead in most highly exposed group was 10.1 µg/dL.
11. Factor-Litvak et al., 1991	No relationship between either mid-trimester maternal blood lead or cord blood lead at birth and birth weight. Mean maternal blood lead in most highly exposed group was 19.0 µg/dL.
12. Nordström et al., 1978b, 1979	125 g deficit in birth weight in offspring of women living close to smelter and of parity ≥3
13. Ward et al., 1987	Negative correlation between placental lead and birth weight
14. Dietrich et al., 1987a; Bornshein et al, 1989	172 g deficit in birth weight associated with maternal blood lead from 10 to 30 µg/dL (mean 8.0 µg/dL)
15. Rhainds et al., 1999	Mean blood lead (1.8 µg/dL) higher in infants weighing <2500 g than in higher weight categories
16. Irgens et al., 1998	Registry study: women occupationally exposed to lead more likely to deliver low birth weight infant than women not exposed to lead (OR 1.3, 95% CI 1.1–1.6)
17. Min et al., 1996	Parental occupational exposure to lead not significantly associated with low birth weight
18. González-Cossio et al., 1997; Hernandez-Avila et al., 2002	Tibial lead (but not patellar or cord blood lead) significantly associated with reduced birth weight and length
19. Hernandez-Avila et al., 2002	Maternal patellar lead associated with low head circumference at 6 months, but not at any of 8 other time points (no control for multiple comparison); blood lead levels 1–35 µg/dL

c. Preterm delivery

The literature on preterm delivery is summarized in Table 3. EPA characterized the results of these studies as contradictory, although there was some evidence of an effect.

Table 3. Lead Exposure of Women and Preterm Delivery

Reference	Findings
1. Fahim et al., 1976	Preterm delivery rate higher in women living near a lead mining community than in control community
2. Angell and Lavery, 1982	No significant association between cord blood lead and gestational age
3. Bellinger et al., 1991	No significant association between cord blood lead and gestational age
4. Needleman et al., 1984	No significant association between cord blood lead and gestational age
5. Rajegowda et al., 1972	No significant association between cord blood lead and gestational age
6. Huel et al., 1981	Significant decrease in gestational age associated with maternal and fetal hair lead in cross-sectional study
7. Moore et al., 1982	Significant decrease in gestational age associated with maternal and cord blood lead in cross-sectional study
8. Ward et al., 1987	Inverse correlation between placental lead and gestational age in cross-sectional study
9. Bornschein et al., 1989	No association between midpregnancy or postpartum maternal blood lead and preterm delivery; prospective study
10. McMichael et al., 1986	Significant relationship between maternal blood lead at delivery and preterm delivery with effect beginning at 7.7–10.6 µg/dL
11. Savitz et al., 1990	Maternal occupational exposure to lead "associated" with preterm delivery (OR 2.3, 95% CI 0.7–7.0)

12. Factor-Litvak et al., 1991	No relationship between either second trimester maternal blood lead or cord blood lead at birth and preterm delivery. Mean maternal blood lead in most highly exposed group was 19.0 µg/dL.
13. Irgens et al., 1998	Registry study: women occupationally exposed to lead more likely to deliver low birth weight infant than women not exposed to lead (OR 1.13, 95% CI 0.98–1.29)
14. Torres-Sánchez et al., 1999	Cord blood lead higher in preterm infants (mean 9.8 µg/dL) than term infants (mean 8.4 µg/dL)

d. Congenital anomalies

Studies on congenital anomalies are summarized in Table 4. These studies, with one exception, do not include biologic measures of lead exposure.

Table 4. Lead Exposure of Women and Congenital Anomalies in the Offspring

Reference	Findings
1. Needleman et al., 1984	Association between cord blood lead and minor, but not major, congenital anomalies (record review)
2. Bound et al., 1997	Case-control study; association between living in area with water lead >10 µg/L and delivering child with neural tube defect
3. Irgens et al., 1998	Registry study: women occupationally exposed to lead more likely to deliver infant with neural tube defect than women not exposed to lead (OR 2.87, 95% CI 1.05–6.38)
4. Jackson et al., 2004	Case-control study; "association" between maternal occupational lead exposure and total anomalous pulmonary venous return (OR 1.57, 95% CI 0.64–3.47)

e. Neurologic and cognitive effects of lead in children

The literature on neurologic and cognitive effects of lead exposure is summarized in Appendix A in tables taken from the EPA Air Criteria Document. According to the EPA summary, there are 7 prospective studies and several meta-analyses that consistently show a strong association between exposure to lead and a decrease in cognitive function of preschool and school age children. An estimated decline of 6.2 IQ points has been associated with an increase in blood lead from 1 to 10 µg/dL. There have been consistent lead-associated decreases in academic and social functioning. EPA is very clear that effects of lead on childhood neurocognitive function have been documented at blood levels ≤10 µg/dL.

Although cord blood or maternal blood lead concentrations have been shown to be associated with a decrease in cognitive test scores in early childhood, as children age, postnatal blood lead levels become more important and the effects of indices of prenatal lead exposure disappear. The EPA document makes the point that lead may be toxic to different brain structures at different developmental times.

2. Experimental animal

The literature on the developmental effects of lead in experimental animals is summarized in Appendix B in tables taken from the EPA Air Quality Criteria for Lead. Lead treatment increases fetal mortality and interferes with growth and development of the offspring. Blood lead concentrations were not measured in dams or fetuses in some studies. Studies in which lead levels were measured suggest that most of the developmental effects of lead occur at maternal lead concentrations >40 µg/dL; however, some studies have shown effects at lead concentrations <20 µg/dL. Malformations have been produced in some studies with maternally toxic lead exposures.

B. Reproductive Toxicity

1. Human

The literature on the male reproductive effects of lead in humans is summarized in Appendix C in tables taken from the EPA Air Quality Criteria for Lead. Lead exposure has been associated with adverse effects on semen parameters and suggestive adverse effects on fertility. According to EPA, these effects occur at blood lead levels >45 μg/dL. Studies on abnormal pregnancy outcome and paternal lead exposure are summarized in Table 5.

Table 5. Adverse Pregnancy Outcome and Paternal Lead Exposure

Reference	Findings
Lindbohm et al., 1991a,b	No association between paternal occupational exposure and spontaneous abortion, except at blood lead levels >30 μg/dL
Alexander, 1996b	No association between employment in lead smelter and spontaneous abortion
Min et al., 1996	Association between paternal occupational lead exposure in the high range and risk of preterm delivery (blood lead >25 μg/dL
Jackson et al., 2004	Paternal occupational lead exposure associated with total anomalous pulmonary venous return (OR 1.83, 95% CI 1.00–3.42)

A time-to-pregnancy study in women did not suggest adverse effects of lead on fecundity at blood lead concentrations <29 μg/dL. Above this level, a longer time to pregnancy was suggested, based on 8 subjects (Sallmén et al., 1995).

2. Experimental animal

The literature on the reproductive effects of lead in experimental animals is summarized in Appendix D in tables taken from the EPA Air Quality Criteria for Lead. Lead treatment causes alterations in the hypothalamic-pituitary-gonadal axis in both sexes and has direct toxic effects on the testis. Blood levels of lead at which adverse reproductive effects occurred, when measured, were typically >40 μg/dL.

C. Human exposure

There is an extensive data base on human lead exposure; the EPA Air Quality Criteria for Lead cites ~200 references on human exposure. Ambient air monitoring of lead is routinely performed in the US by 4 monitoring networks, all of which are funded in whole or in part by EPA, and detailed measurements are available from 1983 to the present. Indoor air concentrations of lead have been shown to be influenced by outdoor air lead, lead-based interior paint, lead in nearby soils, and the presence of tobacco smoke. Ingestion of dust is a more important source of lead in children than is inhalation. Workplace lead concentrations in the absence of lead-based product manufacturing are influenced by factors similar to those influencing residential lead. In manufacturing processes using lead, workplace lead concentrations can be very high, as can be the case during residential renovation, depending on the care taken to contain lead. Exposure of the children of lead workers, called take-home lead" has also been measured.

Soil continues to be an important source of human lead exposure. Soil lead was in the past related to proximity to roadways, because leaded gasoline was the main source of contamination. At present, proximity to deteriorating exterior lead-based paint may be a more important predictor of soil lead. Lead in soil can also be highly elevated near stationary sources of lead emissions such as smelters and battery disposal sites. Exposure to lead in drinking water can occur when lead-based solders were used in the plumbing and when lead leaches from brass fixtures. Lead exposure from food has declined since the removal of lead from automotive gasolines. Lead has

also been found in some calcium supplements, glazes (particularly on imported pottery), imported miniblinds, hair dye, and some herbal or folk remedies.

Blood lead levels in the US from NHANES (2001-2002), expressed in μg/dL as geometric mean and 95% confidence interval, are: age 1-5 years, 1.70 (1.55–1.87); age 6-11 years, 1.25 (1.14–1.36); age 12–19 years, 0.94 (0.90–0.99); age ≥20 years, 1.56 (1.49–1.62).

D. Other relevant studies

1. Toxicokinetic Studies
The EPA Air Quality Criteria for Lead includes a 153-page summary of human toxicokinetics with ~450 references.

2. Authoritative Reviews
Besides the EPA Air Quality Criteria for Lead, there is a draft ATSDR Toxciological Profile for lead, released in September, 2005 (~600 pages).

3. Other reviews
A PubMed search identified 809 review articles on lead of which 96 deal with lead effects during pregnancy.

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Appendix A. Neurologic and Cognitive Effects of Lead
(From the October 2006 EPA Air Quality Criteria for Lead)

Table AX6-2.1. Prospective Longitudinal Cohort Studies of Neurocognitive Ability in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
United States			
Bellinger et al. (1992) U.S.	148 subjects from the Boston Prospective Study were re-evaluated at 10 yrs of age. The WISCR was used to index intellectual status. Extensive assessment of medical and sociodemographic covariates.	Cord and serial postnatal blood Pb assessments Cord blood Pb grouping <3, 6-7, >10 µg/dL Blood Pb at 2 yrs 6.5 (SD 4.9) µg/dL	Increase of 10 µg/dL in blood Pb level at age two was associated with a decrement of ~6 IQ points. Relationship was stronger for verbal compared to performance IQ. Prenatal exposure to Pb as indexed by cord blood Pb levels was unrelated to psychometric intelligence.
Dietrich et al. (1991, 1992, 1993a); Ris et al. (2004) U.S.	253-260 children followed since birth in the Cincinnati Pb Study were re-evaluated at 4, 5, and 6.5 yrs of age. At 4 and 5 yrs, the KABC was used to index intellectual status. At 6.5 yrs, the WISCR was administered. At 15-17 yrs of age, 195 Cincinnati Pb Study subjects were re-evaluated by use of a comprehensive neuropsychological battery that yielded a "Learning/IQ" factor in a principal components analysis. Extensive assessment of medical and sociodemographic covariates.	Prenatal (maternal) and serial postnatal blood Pb assessments Prenatal blood Pb 8.3 (SD 3.7) µg/dL Blood Pb at 2 yrs 17.4 (SD 8.8) µg/dL	Few statistically significant relationships between blood Pb indices and covariate-adjusted KABC scales at 4 and 5 yrs of age. One KABC subscale that assesses visual-spatial skills was associated with late postnatal blood Pb levels following covariate adjustment. After covariate adjustment, avg postnatal blood Pb level was significantly associated with WISCR performance IQ at 6.5 yrs. Blood Pb concentrations >20 µg/dL were associated with deficits in performance IQ on the order of 7 points compared with children with mean blood Pb concentrations <10 µg/dL. At 15-17 yrs, late childhood blood Pb levels were significantly associated with lower covariate-adjusted Learning/IQ factor scores.
Canfield et al. (2003a) U.S.	172 predominantly African-American, lower socioeconomic status children in Rochester, NY followed since they were 5 to 7 mos were evaluated at 3 and 5 yrs. An abbreviated form of the Stanford-Binet Intelligence Scale-4 (SBIS-4) was used to index intellectual status. Extensive assessment of medical and sociodemographic covariates.	Serial postnatal blood Pb Blood Pb at 2 yrs 9.7 µg/dL	Following covariate adjustment, there was a significant inverse relationship between blood Pb indices and IQ at all ages. Overall estimate indicated that an increase in avg lifetime blood Pb concentration of 1 µg/dL was associated with a loss of ½ IQ point. Effects were stronger for subjects whose blood Pb levels never exceeded 10 µg/dL. Semiparametric analysis indicated a decline in IQ of 7.4 points for a lifetime avg blood Pb concentration up to 10 µg/dL, while for levels between 10 and 30 µg/dL a more gradual decrease in IQ was estimated. Authors concluded that the most important aspect of their findings was that effects below 10 µg/dL observed in previous cross-sectional studies have now been confirmed by this rigorous prospective study.
Bellinger and Needleman (2003) U.S.	Reanalysis of data from the Boston Prospective Study focusing on 48 subjects at 10 yrs of age whose blood Pb levels never exceeded 10 µg/dL. WISCR was used to index intellectual status. See	Serial postnatal blood Pb Blood Pb at 2 yrs 6.5 (SD 4.9) µg/dL	IQ was inversely related to two-yr blood Pb levels following covariate adjustment. Blood Pb coefficient (!1.56) was greater than that derived from analyses including children with concentrations above 10 µg/dL (!0.58). Authors conclude that children's IQ scores are reduced at Pb levels still prevalent in

Table AX6-2.1. Prospective Longitudinal Cohort Studies of Neurocognitive Ability in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
	also Bellinger et al. (1992)		U.S.
Chen et al. (2005) U.S.	Repeat measure psychometric data on 780 children enrolled in Treatment of Pb-Exposed Children (TLC) clinical trial were analyzed to determine if blood Pb concentrations at 2 yrs of age constitute a critical period of exposure for expression of later neurodevelopmental deficits. Data for placebo and active drug groups were combined in these analyses, which spanned ~2 to 7 yrs of age. Measures of intellectual status included the Bayley Mental Development Index (MDI) and full scale IQ derived from age-appropriate Wechsler scales.	Blood Pb Range 20-44 µg/dL Baseline blood Pb 26 (SD 26.5) µg/dL in both drug and placebo groups Blood Pb at 7 yrs 8.0 (SD 4.0) µg/dL	Association between blood Pb and psychometric intelligence increased in strength as children became older, whereas the relation between baseline (2 yr) blood Pb and IQ attenuated. Peak blood Pb concentration thus does not fully account for the observed association in older children between their lower blood Pb concentrations and IQ. The effect of concurrent blood Pb on IQ may thusly be greater than currently believed. Authors conclude that these data (a) support the idea that Pb exposure continues to be toxic to children as they reach school age and (b) do not lend support to the interpretation that majority of the damage is done by the time the child reaches 2 to 3 yrs of age.
Europe			
Wasserman et al. (1992, 1994, 2003); Factor- Litvak et al. (1999) Yugoslavia	Birth cohort of ~300-400 infants followed since birth residing in two towns in Kosovo, Yugoslavia, one group near a longstanding Pb smelter and battery manufacturing facility and another in a relatively unexposed location 25 miles away. Intellectual status was monitored from 2 to 10-12 yrs of age with the Bayley Scales of Infant Development, McCarthy Scales of Children's Abilities, and WISCIII. Extensive assessment of medical and sociodemographic covariates.	Maternal prenatal, umbilical cord, and serial postnatal blood Pb Maternal blood Pb in exposed area 19.9 (SD 7.7) µg/dL, unexposed area 5.6 (SD 2.0) µg/dL Umbilical cord blood Pb in exposed area 22.2 (SD 8.1) µg/dL, unexposed area 5.5 (SD 3.3) µg/dL Blood Pb at 2 yrs in exposed area 35.4 µg/dL, unexposed area 8.5 µg/dL	Postnatal blood Pb increment from 10 to 30 µg/dL at 2 yrs of age associated with covariate-adjusted decline of 2.5 points in Bayley MDI. Maternal and cord blood Pb not consistently associated with Bayley outcomes. Higher prenatal and cord blood Pb concentrations associated with lower McCarthy General Cognitive Index (GCI) scores at 4 yrs. Scores on the Perceptual-Performance subscale particularly affected. After covariate-adjustment, children of mothers with prenatal blood Pb levels >20 µg/dL scored a full standard deviation below children in the lowest exposure group (<5 µg/dL prenatal blood Pb). Postnatal blood Pb also associated with poorer performance. Increase in blood Pb level from 10 to 25 µg/dL associated with a reduction of 3.8 points in GCI after covariate-adjustment. Effects even more pronounced on the Perceptual-Performance subscale. At 7 yrs, significant inverse associations between lifetime avg blood Pb and WISCIII IQ were observed, including consistently stronger associations with Performance IQ and later blood Pb measures. Adjusted intellectual loss associated with an increase in lifetime avg blood Pb from 10 to 30 µg/dL was over 4 points in WISCIII Full-Scale and Performance IQ. At 10-12 yrs, subjects were again assessed with the WISCIII. Following covariate-adjustment, avg lifetime blood Pb was associated with all components of the WISCIII, with effect sizes similar to those observed at 7 yrs. In most instances, bone Pb-IQ relationships were stronger than those for blood Pb among subjects residing

Table AX6-2.1. Prospective Longitudinal Cohort Studies of Neurocognitive Ability in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
			near the Pb smelter.
Latin America			
Schnaas et al. (2000) Mexico	112 children followed since birth with complete psychometric data from the Mexico City Prospective Study were examined. Intellectual status indexed by General Cognitive Index (GCI) from McCarthy Scales of Children's Abilities (MSCA). Purpose of the study was to determine if magnitude of the effect of postnatal blood Pb levels on cognition varies with time between blood Pb and cognitive assessments.	Serial postnatal blood Pb Avg blood Pb 24-36 mos 9.7 (range 3-48) µg/dL	A number of significant interactions observed between blood Pb levels and age of assessment. Greatest effect observed at 48 mos, when a 5.8 deficit in adjusted GCI scores was observed for each natural log increment in blood Pb. Authors concluded that four to five yrs of age appears to be a critical period for manifestation of earlier postnatal blood Pb level effects on cognition.
Schnaas et al. (2006) Mexico	From the Mexico City Prospective Study, 150 children followed since birth with complete data for all covariates were examined. Intelligence from age 6 to 10 yrs was assessed using the WISC-R. Blood Pb measurements from various time points, starting from maternal blood Pb levels during the 2nd trimester to postnatal Pb levels at age 10 yrs.	Serial prenatal (maternal) and postnatal blood Pb Geometric mean blood Pb During pregnancy 8.0 (range 1-33) µg/dL Age 1-5 yrs 9.8 (range 2.8-36.4) µg/dL Age 6-10 yrs 6.2 (range 2.2-18.6) µg/dL	Among all the Pb variables at the various time points, only log-transformed blood Pb levels during the 3rd trimester were significantly associated with full scale IQ at ages 6 to 10 yrs, after adjusting for potential confounders. A 3.44 point deficit in full scale IQ was observed for each natural log increment in blood Pb. The authors note that, given the modest sample size and relatively low power of this study, they do not claim that Pb exposure from other developmental period has no effect on child IQ.
Gomaa et al. (2002) Mexico	197 two yr-old children residing in Mexico City followed since birth. Bayley Scales of Infant Development Mental Development Index (MDI) used to index intellectual status. Extensive assessment of medical and sociodemographic covariates.	Umbilical cord and serial postnatal blood Pb Umbilical cord blood Pb 6.7 (SD 3.4) µg/dL Blood Pb at 2 yrs 8.4 (SD 4.6) µg/dL Maternal tibial and patellar bone Pb Patellar (trabecular) bone Pb 17.9 (SD 15.2) µg/g	Umbilical cord blood Pb and patellar (trabecular) bone Pb significantly associated with lower Bayley MDI scores. Maternal trabecular bone Pb levels predicted poorer sensorimotor functioning at two yrs independent of concentration Pb measured in cord blood. Increase in cord blood Pb level from 5 to 10 µg/dL was associated with a 3.1 point decrement in adjusted MDI scores. In relation to lowest quartile of trabecular bone Pb, the 2nd, 3rd, and 4th quartiles were associated with 5.4, 7.2, and 6.5 decrement in MDI following covariate adjustment. Authors concluded that higher maternal trabecular bone Pb levels constitute an independent risk factor for impaired mental development in infancy, likely due to the mobilization of maternal bone Pb stores over gestation.
Téllez-Rojo et al. (2206) Mexico	294 one and two yr-olds residing in Mexico City followed since birth. The Bayley Scales of Infant Development-II (MDI and PDI) were used to index developmental status. There was extensive	Umbilical cord blood Pb and postnatal blood Pb at 12 and 24 mos Umbilical cord blood Pb 4.8 (SD 3.0) µg/dL Blood	Blood Pb at 12 mos was not associated with MDI at either age. Blood Pb at 24 mos was significantly associated with 24 mo MDI. An increase of one logarithmic unit in 24 mo blood Pb level was associated with a reduction of ~5 points in MDI.

Table AX6-2.1. Prospective Longitudinal Cohort Studies of Neurocognitive Ability in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
	assessment of medical and sociodemographic covariates.	Pb at 1 yr 4.27 (SD 2.1) µg/dL Blood Pb at 2 yrs 4.3 (SD 2.2) µg/dL	Findings for PDI were similar. In comparison to a supplemental subsample of 90 subjects with blood Pb levels >10 µg/dL, the coefficient for blood Pb was significantly larger for infants never exceeding that level of internal dose. A steeper inverse slope was observed over the blood Pb range up to 5 µg/dL (!1.71 points per 1 µg/dL increase in blood Pb, p = 0.01) compared to the range between 5 and 10 µg/dL (!0.94 points, p = 0.12); however, these slopes were not significantly different (p = 0.34). In conclusion, a major finding of this prospective study was that a significant inverse relationship between blood Pb concentration and neurodevelopment was observed among children whose blood Pb levels did not exceed 10 µg/dL at any age.
Australia			
Baghurst et al. (1992); McMichael et al. (1994); Tong et al. (1996) Australia	400-500 subjects residing in and near Port Pirie, Australia and followed since birth were re-evaluated at 7 to 8 and 11-13 yrs of age. WISCR was used to index intellectual status at both ages. Extensive assessment of medical and sociodemographic covariates.	Maternal prenatal, umbilical cord and serial postnatal blood Pb Antenatal avg blood Pb 10.1 (SD 3.9) µg/dL Umbilical cord blood Pb 9.4 (SD 3.9) µg/dL Blood Pb at 2 yrs geometric mean 21.3 (SD 1.2) µg/dL Deciduous central incisor whole tooth Pb Tooth Pb geometric 8.8 (SD 1.9) µg/g	Significant decrements in covariate-adjusted full scale IQ were observed in relationship to postnatal blood Pb levels at both ages. At 7 to 8 yrs of age a loss of 5.3 points was associated with an increase in blood Pb from 10 to 30 µg/dL. At 11-13 yrs, mean full scale IQ declined by 3.0 points for an increase in lifetime avg blood Pb concentrations from 10 to 20 µg/dL. Pb levels in central upper incisors were also associated with lower 7-8 yr IQ following covariate adjustment. Adjusted estimated decline in IQ across the range of tooth Pb from 3 to 22 ppm was 5.1 points.
Cooney et al. (1991) Australia	175 subjects from the Sydney, Australia Prospective Study were assessed at 7 yrs of age. The WISCR was used to index intellectual status. Extensive assessment of medical and sociodemographic characteristics.	Maternal and cord blood Pb Cord blood Pb 8.4 µg/dL (SD not given) Blood Pb at 2 yr 15.8 µg/dL (SD not given)	Blood indices of Pb exposure were not associated with any measure of psychometric intelligence. Authors conclude that the evidence from their study indicates that if developmental deficits do occur at blood Pb levels <25 µg/dL, the effect size is likely to be small (<5%). Sydney results are difficult to interpret from the statistical presentation in their report. It is not clear which covariates were entered into regression analyses nor is the empirical or substantive basis for their conclusion.
Asia			
Shen et al. (1998) China	Pregnant women and newborns in Shanghai, China recruited from health care facilities in the community on the basis of cord blood Pb concentration percentiles (30th and 70th) yielding a	Cord blood Pb "High group" 13.4 (SD 2.0) µg/dL "Low group" 5.3 (SD 1.4) µg/dL Blood Pb at 1 yr "High group"	At all ages the Bayley MDI was associated with cord blood Pb groupings following adjustment for covariates. Postnatal blood Pb unrelated to any Bayley measures. Differences in MDI between prenatal blood Pb exposure groupings generally in

Table AX6-2.1. Prospective Longitudinal Cohort Studies of Neurocognitive Ability in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
	total N of 173 subjects. The Bayley Scales of Infant Development Mental Development Index (MDI) and Psychomotor Development Index (PDI) were used to index sensorimotor/intellectual status at 3, 6, and 12 mos. Extensive assessment of medical and sociodemographic characteristics.	14.9 (SD 8.7) µg/dL "Low group" 14.4 (SD 7.7) µg/dL	accord with similar investigations in Boston, Cincinnati, and Cleveland. Authors conclude that the adverse effects of prenatal Pb exposure are readily discernible and stable over the first yr of life.

Table AX6-2.2. Meta- and Pooled-Analyses of Neurocognitive Ability in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
Lanphear et al. (2005)	Pooled analysis of seven international prospective studies involving 1,333 school-age children. Primary outcome measure was full-scale IQ as assessed by age-appropriate Wechsler scale. Measures of exposure were concurrent, peak, avg lifetime and "early" blood Pb (i.e. mean blood Pb from 6-24 mos). Cord blood Pb was also investigated for those studies that collected these samples at birth. Multivariate regression models were developed adjusting for site as well as 10 common covariates. Blood Pb measure with the largest adjusted R2 was nominated a priori as the preferred index for relating Pb exposure to IQ in subsequent analyses. Results evaluated by applying a random-effects model.	Concurrent blood Pb Serial postnatal blood Pb Lifetime avg blood Pb 12.4 (range 4.1-34.8) µg/dL	Umbilical cord blood Pb level exhibited the strongest relationship with IQ, although results of regression analyses for all blood Pb variables were similar. Steepest declines in IQ were at blood Pb concentrations below 10 µg/dL. For the entire pooled data set, a decline of 6.2 IQ points (95% CI: 3.8, 8.6) was estimated for an increment in blood Pb from 1 to 10 µg/dL.
Needleman and Gatsonis (1990)	Meta analysis of 12 studies chosen on the basis of quality—covariate assessment and application of multiple regression techniques. Studies weighted on basis of sample size. Studies divided according to tissue analyzed (blood or teeth). Joint p-values and avg effect sizes calculated using two different methods.	Blood Pb Tooth Pb	Joint p-values for blood Pb studies were <0.0001 for both methods, whereas joint p-values of <0.0006 and <0.004 were obtained for teeth. Partial correlations ranged from –0.27 to –0.0003. No single study was responsible for the significance of the final findings. Authors concluded that the hypothesis that Pb lowers children's IQ at relatively low dose is strongly supported by results of this quantitative review.
Schwartz (1994)	Meta analysis of 7 recent studies relating blood Pb to IQ were reviewed, three longitudinal and four cross-sectional. Measure of effect was estimated decrease in IQ for an increase in blood Pb from 10 to 20 µg/dL. Studies were weighted by the inverse of the variances using random	Blood Pb	Estimated decrease in IQ per blood Pb increment from 10 to 20 µg/dL was –2.6 points (SE 0.41). Results were not determined by any individual study. Effect estimates were similar for longitudinal and cross-sectional studies. For studies with mean blood Pb levels <15 µg/dL, estimated effect sizes were larger. When the study with the lowest exposures was examined alone using nonparametric smoothing (Boston), no evidence of a threshold was observed down to a blood Pb level of 1 µg/dL. Author concludes that these data provide further evidence of Pb effects on cognition at levels below 10 µg/dL.
Pocock et al. (1994)	Meta-analysis of five prospective and fourteen cross-sectional studies (including tooth and blood tissues) were included. The fixed effect method of Thompson and Pocock (1992) was employed. Only blood Pb at or near two yrs of age was considered for the prospective studies.	Blood Pb Tooth Pb	Overall conclusion was that a doubling of blood Pb levels from 10 to 20 µg/dL, or tooth Pb from 5 to 10 µg/g was associated with an avg estimated deficit in IQ of ~1-2 points. Authors caution interpretation of these results and Pb literature in general, citing questions about representativeness of the samples, residual confounding, selection bias, and reverse causality.

Table AX6-2.3. Cross-Sectional Studies of Neurocognitive Ability in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
United States			
Lanphear et al. (2000) U.S.	4,853 U.S. children ages six to 16 yrs enrolled in NHANES-III. Two subtests of the WISC-R (Block Design and Digit Span) used to assess intellectual status. Medical and sociodemographic covariates were assessed	Blood Pb at time of testing Geometric blood Pb 1.9 (SE 0.1) µg/dL 2.1% with blood Pb 10 µg/dL	Multivariate analyses revealed a significant association between blood Pb levels and both WISC-R subtests. Associations remained statistically significant when analyses were restricted to children with blood Pb levels below 10 µg/dL. Authors caution that lack of control for parental intelligence and variables like the HOME scale should temper any conclusions regarding observed effects.
Emory et al. (2003) U.S.	77 healthy, lower-risk African-American infants age 7 mos. The Fagan Test of Infant Intelligence (FTII) was administered to assess intellectual status. Birth weight and gestational age examined as potential covariates/confounders	Maternal blood Pb Blood Pb 0.72 (SD 0.86) µg/dL	Infants scoring in the upper 5th to 15th percentiles for the FTII had mother with significantly lower maternal blood Pb levels when compared to those scoring in the lower 5th or 15th percentile. Findings of this study should be considered preliminary due to small sample size and lack of covariate assessment or control.
Chiodo et al. (2004) U.S.	237 African-American inner-city children assessed at 7.5 yrs of age. Cohort was derived from a larger study of the effects of prenatal alcohol exposure on child development. 83% of children in Pb study had little or no gestational exposure to alcohol. WISC-III was administered to assess intellectual status. Medical and sociodemographic covariates were assessed.	Blood Pb at time of testing Blood Pb 5.4 (SD 3.3) µg/dL	Following covariate adjustment statistically significant relationships between blood Pb and full-scale, verbal and performance IQ were observed. Significant effects of Pb on full-scale and performance IQ was evident at blood Pb concentrations below 7.5 µg/dL.
Europe			
Walkowiak et al. (1998) Germany	384 six-yr-old children in three German cities. Two subtests of the WISC (Vocabulary and Block Design) used to estimate IQ. Both subscales were combined to form a "WISC Index." Medical and sociodemographic covariate covariates were assessed.	Blood Pb at time of testing Blood Pb 4.2 µg/dL 95th percentile 8.9 µg/dL	Following covariate-adjustment, WISC Vocabulary was significantly associated with blood Pb but combined WISC index was borderline. Authors conclude that findings roughly correspond with those of other studies that find effects below 10 µg/dL but caution that potentially important covariates such as HOME scores were not controlled.
Prpic-Majic et al. (2000) Croatia	275 3rd and 4th grade students in Zagreb, Croatia. WISC-R was administered to assess intellectual status. Covariate factors limited to parents' educational status and gender of child.	Blood Pb at time of testing Blood Pb 7.1 (SD 1.8) µg/dL	Following covariate adjustment, no statistically significant associations were observed for Pb or other indicators of toxicity (ALAD, EP) on WISC-R. Authors argue that study had sufficient power and that the "no-effect" threshold for Pb must be in the upper part or above the study's range of exposures.
Latin America			
Kordas et al. (2004, 2006) Mexico	602 1st grade children in public schools in a highly industrialized area of northern Mexico. Premise of	Blood Pb at time of testing Blood Pb 11.5 (SD 6.1) µg/dL	Following covariate adjustment blood Pb levels were significantly associated with poorer performance on the PPVT-

Table AX6-2.3. Cross-Sectional Studies of Neurocognitive Ability in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
	study was that effects of Pb could be explained by correlated nutritional factors such as iron status, anemia, and growth. Peabody Picture Vocabulary Test-Revised (PPVT-R), Cognitive Abilities Test (CAT), and an abbreviated form of the WISC-R were administered to assess intellectual status. Medical and sociodemographic covariates were assessed.		R, WISC-R Coding, and Number and Letter Sequencing, a Math Achievement Test, and the Sternberg Memory Test. Authors concluded that Pb's association with iron deficiency anemia or growth retardation could not explain relationship between Pb and cognitive performance. Non-linear analyses of selected neurocognitive outcomes revealed that dose-response curves were steeper at lower than at higher blood Pb levels. Moreover, the slopes appeared negative at blood Pb levels below 10 µg/dL, above which they tend to plateau. Effects of Pb on neurocognitive attainment appeared to be greatest among the least advantaged members of the cohort.
Counter et al. (1998) Ecuador	77 chronically Pb-exposed children living in Ecuadorian villages where Pb is used extensively in commercial ceramics production. Ravens Colored Progressive Matrices (RCPM) used to index intellectual status. Only half of the sample was assessed. No assessment of medical or sociodemographic covariates.	Blood Pb at time of testing Blood Pb 47.4 (SD 22) µg/dL	Simple regression analysis revealed a correlation between blood Pb and RCPM of only borderline significance. Results difficult to interpret because there was no attempt to age-adjust. When analysis restricted to children 9 to 11 yrs of age, a highly significant negative correlation was obtained. Study has little relevance to the question of Pb hazards in the U.S. because of unusually high levels of exposure.
Asia			
Rabinowitz et al. (1991) Taiwan	443 children in grades one to three in Taipei City and three schools near Pb smelters. Ravens Colored Progressive Matrices (RCPM) used to index intellectual status. Medical and sociodemographic covariate factors were assessed.	Dentin tooth Pb Taipei City 4.3 (SD 3.7) µg/g Smelter areas 6.3 (SD 3.3) µg/g	Scores on the RCPM were negatively correlated with tooth Pb concentrations. In multivariate analyses, parental education was the most important predictor of RCPM scores, but tooth Pb concentrations still significantly predicted lower scores in females residing in low-income families.
Bellinger et al. (2005) India	74 four to fourteen yr-old children residing in Chennai, India were enrolled in the study, 31 of which were assessed with the Binet-Kamath Intelligence test. Data were collected on sociodemographic features of subjects' families.	Blood Pb at time of testing Blood Pb 11.1 (SD 5.6) µg/dL	Covariate-adjusted blood Pb coefficient was negative but nonsignificant, perhaps due to small sample size and highly variable performance of subjects with the least elevated blood Pb concentrations.
Middle East			
Al-Saleh et al. (2001) Saudi Arabia	533 Riyadh, Saudi Arabian girls (6-12 yrs of age) were administered a variety of standardized tests including the TONI, and the Beery VMI. Extensive data were collected on potentially confounding variables including sociodemographic variables, early developmental milestones and child health status.	Blood Pb at time of testing Blood Pb 8.1 (SD 3.5) µg/dL	Blood Pb levels had no impact on TONI scores but this test has limited evidence of validity in this population. Significant negative associations were noted between blood Pb levels and the Beery VMI suggesting an association between impairment in visual-spatial skills in Saudi children with blood Pb levels in the range of 2.3 to 27.4 µg/dL.

Table AX6-2.4. Effects of Lead on Academic Achievement in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
United States			
Lanphear et al. (2000) U.S.	Design: Cross-sectional. 4,853 U.S. children ages six to 16 yrs enrolled in NHANES-III. Subjects were administered the Arithmetic and Reading subtests of the Wide Range Achievement Test-Revised (WRATR). A number of medical and sociodemographic covariates were assessed and entered into multivariable models.	Blood Pb at time of testing Geometric blood Pb 1.9 (SE 0.1) µg/dL 2.1% with blood Pb □10 µg/dL	Following covariate adjustment, a statistically significant relationship between blood Pb and WRATR performance was found. A 0.70 point decrement in Arithmetic scores and a 1 point decrement in Reading scores for each 1 µg/dL increase in blood Pb concentration was observed. Statistically significant inverse relationships between blood Pb levels and performance for both Reading and Arithmetic subtests were found for children with blood Pb concentrations <5 µg/dL. Authors concluded that results of these analyses suggest that deficits in academic skills are associated with blood Pb concentrations lower than 5 µg/dL. They cautioned, however, that two covariates that have been shown to be important in other Pb studies (i.e., parental IQ and HOME scores) were not available. This may have over or under estimated deficits in academic skills related to Pb. They further caution that, as with all cross-sectional studies utilizing blood Pb as the index of dose it is not clear whether deficits in academic skills were due to Pb exposure that occurred sometime during early childhood or due to concurrent exposure. Nevertheless, concurrent blood Pb levels reflect both ongoing exposure and preexisting body burden.
Needleman et al. (1990) U.S.	Design: Prospective cohort. Re-examination of the Chelsea and Somerville cohort recruited in the 1970's (Needleman et al., 1979). 132 adolescents were recalled. Large battery of tests was administered to examine neurobehavioral deficits and academic achievement in high school and shortly following graduation. Extensive assessment of medical and sociodemographic covariates.	Tooth (dentin) Pb Tooth Pb median 8.2 µg/g	Subjects with dentin Pb levels >20 ppm were at higher risk of dropping out of high school (adjusted OR = 5.8 [95% CI: 1.4, 40.7]) and of having a reading disability (adjusted OR = 5.8 [95% CI: 1.7, 19.7]). Higher dentin Pb levels were also significantly associated with lower class standing, increased absenteeism, and lower vocabulary and grammatical reasoning scores on the Neurobehavioral Evaluation System (NES). Authors conclude that undue exposure to Pb has enduring and important effects on objective parameters of success in life.
Bellinger et al. (1992) U.S.	Design: Prospective longitudinal. 148 children in the Boston Pb Study cohort were examined at 10 yrs of age. The short-form of the Kaufman Test of Educational Achievement (KTEA) was used to assess academic achievement. Primary outcome was the Battery Composite Score. Extensive assessment of medical and sociodemographic covariates.	Cord and serial postnatal blood Pb assessments. Cord blood Pb grouping <3, 6-7, >10 µg/dL Blood Pb at 2 yrs 6.5 (SD 4.9) µg/dL	After covariate-adjustment, blood Pb levels at 24 mos were significantly predictive of lower academic achievement (□ = !0.51, SE 0.20). Battery Composite Scores declined by 8.9 points for each 10 µg/dL increase in blood Pb. This association was significant after adjustment for IQ. Authors conclude that Pb-sensitive neuropsychological processing and learning factors not reflected in measures of global intelligence may contribute to deficits in academic achievement.
Leviton et al. (1993)	Design: Prospective cohort. Teachers of ~2000	Cord blood Pb Cord blood Pb	Following adjustment for potential confounding variables,

Table AX6-2.4. Effects of Lead on Academic Achievement in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
U.S.	eight yr-old children born in 1 hospital in Boston between 1979 and 1980 filled out the Boston Teachers Questionnaire (BTQ) to assess academic performance and behavior. Limited information is provided on the assessment of covariate factors but a number were considered and controlled for in multivariable analyses.	6.8 µg/dL Tooth (dentin) Pb Tooth Pb 2.8 µg/g	elevated dentin Pb concentrations were associated with statistically significant reading and spelling difficulties as assessed by the BTQ among girls in the sample. Authors conclude that their findings support the case for Pb-associated learning problems at levels that were prevalent at that time in the general population. However, authors add that the inability to assess child-rearing quality in this study conducted by mail limits the inferences that can be drawn.
Australia			
Fergusson et al. (1993, 1997); Fergusson and Horwood (1993) New Zealand	Design: Prospective cohort. Academic performance was examined in a birth cohort of 1200 New Zealand children enrolled in the Christchurch Health and Development Study. Measures of academic performance at 12-13 yrs included the Brut Reading Test, Progressive Achievement Test, Test of Scholastic Abilities, and teacher ratings of classroom performance in the areas of reading, writing, and mathematics. The growth of word recognition skills from 8 to 12 yrs was also examined using growth curve modeling methods. Academic achievement in relationship to Pb was re-examined in this cohort at 18 yrs. Measures of academic achievement included the Burt Reading Test, number of yrs of secondary education, number of certificates passed (based on national examinations), and leaving school without formal qualifications (failing to graduate). Extensive assessment of medical and social covariates.	Tooth (dentin) Pb Tooth Pb 6.2 (SD 6.2) µg/g	Following covariate adjustment, dentin Pb levels were significantly associated with virtually every formal index of academic skills and teacher ratings of classroom performance in 12-13 yr-olds. After adjustment for covariates, tooth Pb levels greater than 8 µg/g were associated with significantly slow growth in word recognition abilities with no evidence of catch up. At 18 yrs, tooth Pb levels were significantly associated with lower reading test scores, having a reading level of less than 12 yrs, failing to complete three yrs of high school, leaving school without qualifications, and mean number of School Certificates passed. Authors conclude that early exposure to Pb is independently associated with detectable and enduring deficits in children's academic abilities. They further conclude that their findings are particularly significant in that they confirm the findings of Needleman (1990), albeit in a cohort with lower levels of exposure to environmental Pb.
Asia			
Wang et al. (2002a) Taiwan	Design: Cross-sectional. 934 3rd graders living in an urban industrial area of Taiwan. Outcome variables were grades for Chinese (reading, writing), mathematics, history, and natural science. Grades were converted into individual class rankings to avoid teacher bias. Limited data on medical and sociodemographic covariates.	Blood Pb at time of evaluation Blood Pb 5.5 (SD 1.9) µg/dL	Following covariate adjustment, blood Pb was significantly associated with lower class ranking in all academic subjects. Major shortcoming of this study is lack of control for potentially important covariates such as parental IQ. However, the relatively low levels of exposure in this sample and strength and consistency of the reported relationships suggest that Pb may be playing some role in lowering academic performance.
Rabinowitz et al. (1992) Taiwan	Design: Cross-sectional. Teachers of 493 children in grades 1-3 filled out the Boston Teachers Questionnaire (BTQ) to assess academic performance and behavior. Sociodemographic and medical covariate factors were assessed.	Tooth (dentin) Pb Tooth Pb 4.6 (SD 3.5) µg/g	Prior to adjustment for covariates, girls with higher exposures to Pb evinced a borderline significant trend for reading difficulties while byes displayed significantly increased difficulties with respect to activity levels and task attentiveness. In logistic regression models that include significant covariate factors, the

Table AX6-2.4. Effects of Lead on Academic Achievement in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
			tooth Pb terms failed to achieve statistical significance. Authors conclude that Pb levels found in the teeth of children in this Taiwanese sample are not associated with learning problems as assessed by the BTQ.
Middle East			
Al Saleh et al. (2001) Saudi Arabia	Class rank, as assessed by the teacher, was examined in conjunction with blood Pb levels in 533 Riyadh, Saudi Arabian girls (6-12 yrs of age). Extensive data were collected on potentially confounding variables including sociodemographic variables, early developmental milestones and child health status.	Blood Pb at time of testing Blood Pb 8.1 (SD 3.5) µg/dL	A significant inverse relationship between blood Pb levels and rank percentile scores was observed after adjusting for a number of demographic and socioeconomic variables. When multiple regression models were fitted to a subset of students with blood Pb levels below 10 µg/dL, class rank percentile continued to show a statistically significant association with blood Pb levels.

Table AX6-2.5. Effects of Lead on Specific Cognitive Abilities in Children — Attention/Executive Functions, Learning, and Visual-spatial Skills

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
United States			
Bellinger et al. (1994a) U.S.	Design: Prospective cohort. 79 subjects from the original Chelsea and Somerville, MA Pb study were re-evaluated at 19-20 yrs of age with the Mirsky battery of attentional measures. Extensive measures of medical and sociodemographic covariates.	Tooth (dentin) Pb Tooth Pb 13.7 (SD 11.2) µg/g KXRF Bone Pb Tibial bone Pb (range <1 - >10) µg/g Patellar bone Pb (range <1 - >15) µg/g	Higher tooth Pb concentrations were significantly associated with poorer scores on the Focus-Execute and Shift factors of the Mirsky battery. Few significant associations were observed between bone Pb levels and performance. Authors conclude that early Pb exposure may be associated with poorer performance on executive/regulatory functions, which are thought to depend on the frontal or prefrontal regions of the brain.
Stiles and Bellinger (1993) U.S.	Design: Prospective longitudinal. 148 subjects from the Boston Pb Study were re-evaluated at 10 yrs of age with an extensive neuropsychological battery. Tests included the California Verbal Learning Test, Wisconsin Card Sorting Test, Test of Visual-Motor Integration, Rey-Osterieth Complex Figure, Story Recall, Finger Tapping, and Grooved Pegboard. Extensive measures of medical and sociodemographic covariates.	Cord and serial postnatal blood Pb assessments Cord blood Pb grouping <3, 6-7, >10 µg/dL Blood Pb at 2 yrs 6.5 (SD 4.9) µg/dL	Authors point out that the number of significant associations was about equal to those that would be expected by chance. However, tasks that assess attentional behaviors and executive functions tended to among those for which Pb was a significant predictor of performance. Following covariate adjustment, higher blood Pb concentrations at two yr were significantly associated with lower scores on Freedom from Distractibility factor of the Wechsler scales, increase in percentage of perseverative errors on the Wisconsin Card Sorting Test and the California Verbal Learning Test.
Canfield et al. (2003b, 2004) U.S.	Design: Prospective longitudinal. 170-174 children from the Rochester Pb Study were administered a number of learning and neuropsychological functioning at 48, 54, and 66 mos of age. At 48 and 54 mos the Espy Shape School Task was administered while at 66 mos the Working Memory and Planning assessment protocols of the Cambridge Neuropsychological Test Automated Battery (CANTAB) was given. Extensive measures on medical and sociodemographic covariates.	Serial postnatal blood Pb Blood Pb at 2 yrs 9.7 µg/dL Lifetime avg blood Pb 7.2 (range 0-20) µg/dL	Following covariate adjustment, blood Pb level at 48 mos was negatively associated with children's focused attention while performing the Shape School Tasks, efficiency at naming colors, and inhibition of automatic responding. Children with higher blood Pb concentrations also completed fewer phases of the Espy tasks and knew fewer color and shape names. On the CANTAB battery, children with higher lifetime avg blood Pb levels showed impaired performance on spatial working memory, spatial memory span, and cognitive flexibility and planning. Authors conclude that the effects of pediatric Pb exposure are not restricted to global measures of intellectual functioning and executive processes may be at particular risk.

Table AX6-2.5. Effects of Lead on Specific Cognitive Abilities in Children — Attention/Executive Functions, Learning, and Visual-spatial Skills

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
Ris et al. (2004) U.S.	Design: Prospective longitudinal. 195 subjects from the Cincinnati Pb Study were administered an extensive and comprehensive neuropsychological battery at 16-17 yrs of age. Domains assessed included Executive Functions, Attention, Memory, Achievement, Verbal Skills, Visuoconstructional, and Fine Motor. Factor scores transformed to ranks derived from a principal components factor analysis of the neuropsychological test scores were the primary outcome variables. Extensive measures on medical and sociodemographic covariates.	Prenatal (maternal) and serial postnatal blood Pb assessments Prenatal blood Pb 8.3 (SD 3.7) µg/dL Blood Pb at 2 yrs 17.4 (SD 8.8) µg/dL	Following covariate adjustment, strongest associations between Pb exposure and performance were observed for factor scores derived from the Attention component, which included high loadings on variables from the Conners Continuous Performance Test. This relationship was strongest in males. Authors speculate that since the incidence of Attention Deficit/Hyperactivity Disorder is greater in males in general, early exposure to Pb may exacerbate a latent potential for such problems.

Table AX6-2.6. Effects of Lead on Disturbances in Behavior, Mood, and Social Conduct in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
United States			
Sciarillo et al. (1992) U.S.	Design: Cross-sectional. 150 2-5 yr-old children in Baltimore separated into "high" (2 consecutive blood Pb levels >15 µg/dL) and "low" groups. Mothers filled out the Achenbach Child Behavior Checklist (CBCL). The Center for Epidemiologic Studies Depression Scale (CESD) was administered to mothers as a control measure.	Screening blood Pbs at various times before assessment High group 28.6 (SD 9.3) µg/dL Low group 11.3 (SD 4.3) µg/dL	When compared to lower exposed group, children in the high group had a significantly higher CBCL Total Behavior Problems Score (TBPS) and Internalizing and Externalizing scores. After adjustment for maternal depression, blood Pb concentrations were still significantly associated with an increase in the TBPS. Children in high group were nearly 3 times more likely to have a TBPS in the clinical range. A significantly higher percentage of children in the high group scored in the clinical range for CBCL subscales measuring aggressive and destructive behavioral tendencies.
Bellinger et al. (1994b) U.S.	Design: Prospective cohort: 1782 children born within a 1-yr period at a single Boston hospital were examined at 8 yrs of age. Teachers filled out the Achenbach Child Behavior Profile (ACBP). Medical and sociodemographic characteristics assessed by questionnaire and chart review.	Umbilical cord blood Pb Cord blood Pb 6.8 (SD 3.1) µg/dL Tooth (dentin) Pb Tooth Pb 3.4 (SD 2.4) µg/g	Cord blood Pb levels were not associated with the prevalence or nature of behavioral problems reported by teachers. Tooth Pb levels were significantly associated with ACBP Total Problem Behavior Scores (TPBS). Statistically significant tooth Pb-associated increases in both Externalizing and Internalizing scores were observed. Each log unit increase in tooth Pb was associated with a 1.5-point increase in T scores for these scales. Authors caution that residual confounding cannot be ruled out because of the lack of information on parental psychopathology or observations of the family environment. However, these results are in accord with other studies that social and emotional dysfunction may be an important expression of elevated Pb levels during early childhood.
Denno (1990) U.S.	Design: Prospective cohort. Survey of 987 Philadelphia African-American youths enrolled in the Collaborative Perinatal Project. Data available from birth through 22 yrs of age. Analysis considered 100 predictors of violent and chronic delinquent behavior.	Blood Pb Values not provided	Repeat offenders presented consistent features such as low maternal education, prolonged male-provider unemployment, frequent moves, and higher Pb intoxication. In male subjects, a history of Pb poisoning was among the most significant predictors of delinquency and adult criminality.
Needleman et al. (1996) U.S.	Design: Prospective cohort. 850 boys enrolled in the Pittsburgh Youth Study were prescreened to assess delinquent behavioral tendencies. Subjects who scored in the 30th percentile on the risk score and an equal number randomly selected from the remainder form the sample of 530 subjects. Measures of antisocial behavior were administered at 7 and 11 yrs of age including the Self Reported Antisocial Behavior scale (SRA), Self Report of	Bone Pb by K-XRF Bone Pb (exact concentrations not reported) Negative values treated categorically as 1 and positive values grouped into quintiles.	Following covariate-adjustment, parents of subjects with higher Pb levels in bone reported significantly more somatic complaints, more delinquent and aggressive behavior, and higher Internalizing and Externalizing scores. Teachers reported significant increase in scores on somatic complaints, anxious/depressed, social problems, attention problems, delinquent behavior, aggressive behavior, internalizing and externalizing problems in the higher bone Pb subjects. At 11 yrs, subject's SRD scores were also significantly related to bone

Table AX6-2.6. Effects of Lead on Disturbances in Behavior, Mood, and Social Conduct in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
	Delinquent Behavior (SRD), and parents' and teachers' versions of the Achenbach Child Behavior Profile (CBCL). Extensive assessment of medical and sociodemographic covariates.		Pb levels. More high Pb subjects had CBCL T scores in the clinical range for attention, aggression, and delinquency. Authors conclude that Pb exposure is associated with increased risk for antisocial and delinquent behavior.
Dietrich et al. (2001) U.S.	Design: Prospective longitudinal. 195 subjects from the Cincinnati Pb Study were examined at 16-17 yrs of age. Parents were administered a questionnaire developed specifically for the study while CLS subjects were given the Self Report of Delinquent Behavior. Extensive assessment of medical and sociodemographic covariates.	Prenatal (maternal) and serial postnatal blood Pb assessments. Prenatal blood Pb 8.3 (SD 3.7) µg/dL Blood Pb at 2 yrs 17.4 (SD 8.8) µg/dL	Prenatal (maternal) blood Pb was significantly associated with a covariate-adjusted increase in the frequency of parent-reported delinquent and antisocial acts. Prenatal and measures of postnatal Pb exposure were significantly associated with self-reported delinquent and antisocial behaviors. Authors concluded that Pb might play a measurable role in the development of behavioral problems in inner-city children independent of other important social and biomedical cofactors.
Needleman et al. (2002) U.S.	Design: Case-control. 194 adjudicated delinquents and 146 non-delinquent controls recruited from high schools in the City of Pittsburgh and Allegheny County, PA. Covariate assessments were not extensive but did include race, parental sociodemographic factors, and neighborhood crime rates.	Bone Pb by KXRF Cases 11.0 (SD 32.7) µg/g Controls 1.5 (SD 32.1) µg/g	Cases had significantly higher avg concentrations of Pb in tibia than controls. Following covariate adjustment, adjudicated delinquents were 4 times more likely to have bone Pb concentration >25 µg/g then controls. Bone Pb level was the second strongest factor in the logistic regression models, exceeded only by race. In models stratified by race, bone Pb was exceeded as a risk factor only by single parent status. Authors conclude that elevated body Pb burdens are associated with increased risk for adjudicated delinquency.
Europe			
Wasserman et al. (1994) Yugoslavia	Design: Prospective longitudinal. Birth cohort of ~300-400 infants followed since birth residing in two towns in Kosovo, Yugoslavia, one group near a longstanding Pb smelter and battery manufacturing facility and another in a relatively unexposed location 25 miles away. 379 children at 3 yrs of age were examined. Parents were interviewed with the Achenbach Child Behavior Checklist (CBCL). Extensive assessment of medical and sociodemographic covariates.	Maternal prenatal, umbilical cord and serial postnatal blood Pb Maternal blood Pb in exposed area 19.9(SD 7.7) µg/dL, unexposed area 5.6 (SD 2.0) µg/dL Umbilical cord blood Pb in exposed area 22.2 (SD 8.1) µg/dL, unexposed area 5.5 (SD 3.3) µg/dL Blood Pb at 2 yrs in exposed area 35.4 µg/dL, unexposed area 8.5 µg/dL	Following covariate adjustment, concurrent blood Pb levels were associated with increased Destructive Behaviors on the CBCL subscale, although the variance accounted for by Pb was small compared to sociodemographic factors. As blood Pb increased from 10 to 20 µg/dL, subscale scores increased by 0.5 points. The authors conclude that while statistically significant, the contribution of Pb to social behavioral problems in this cohort was small compared to the effects of correlated social factors.
Australia			
Burns et al. (1999)	Design: Prospective longitudinal. 322 subjects	Maternal prenatal, umbilical	After adjustment for covariates, regression models revealed that

Table AX6-2.6. Effects of Lead on Disturbances in Behavior, Mood, and Social Conduct in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
Australia	residing in and near Port Pirie, Australia and followed since birth were re-evaluated at 11-13 yrs of age. Parents completed the Achenbach Child Behavior Checklist. Extensive assessment of medical and sociodemographic characteristics.	cord and serial postnatal blood Pb Antenatal avg blood Pb 10.1 (SD 3.9) µg/dL Umbilical cord blood Pb 9.4 (SD 3.9) µg/dL Blood Pb at 2 yrs geometric mean 21.3 (SD 1.2) µg/dL	for an increase in avg lifetime blood Pb concentrations from 10 to 30 µg/dL, the Externalizing behavior problem T score increased by 3.5 points in boys (95% CI: 1.6, 5.4), but only 1.8 points (95% CI: !0.1, 11.1) in girls. Internalizing behavior problems were predicted to rise by 2.1 points (95% CI: 0.0, 4.2) in girls by only 0.8 (95% CI: !0.9, 2.4) in boys. Authors concluded that Pb exposure is associated with an increase in externalizing (undercontrolled) behaviors in boys.
Fergusson et al. (1993) New Zealand	Design: Prospective cohort. 690-891 children ages 12 and 13 yrs from the Christchurch Child and Health Study, New Zealand were examined. Mothers and teachers were asked to respond to a series of items derived from the Rutter and Conners parental and teacher questionnaires. Extensive assessment of sociodemographic and medical covariates.	Tooth (dentine) Pb Tooth Pb range 3–12 µg/g	Statistically significant dose-effect relationships were observed between tooth Pb levels and the inattention/restlessness variable at each age. Authors conclude that this evidence is consistent with the view that mildly elevated Pb levels are associated with small but long term deficits in attentional behaviors.
Silva et al. (1988) New Zealand	As part of the 11-yr follow-up of the Dunedin Multidisciplinary Health and Development Study, a longitudinal study of a birth cohort of children born in Dunedin's only obstetric hospital, blood Pb levels were measured in 579 children at age 11 yrs old. The study sample was over-representative of higher SES, but was found to be representative of Dunedin children in educational attainment. Blood Pb levels were examined in association with intelligence assessed using the WISC-R and behavioral problems as assessed by both parents and teachers.	Blood Pb at time of testing Blood Pb at age 11 yrs 11.1 (SD 4.91, range 4-50) µg/dL	Log blood Pb levels were significantly correlated with most measures of behavioral problems, including the Parents' and Teachers' Rutter Behavioral Scale, the Parents' and Teachers' Hyperactivity Scale, and the Teachers' Inattention Scale, after adjustment for various potential confounders. No associations were observed between log blood Pb levels and IQ. Authors concluded that exposure to Pb is associated with increases in children's' general behavioral problems, especially in inattention and hyperactivity.

Table AX6-2.7. Effects of Lead on Sensory Acuities in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
United States			
Schwartz and Otto (1991) U.S.	Design: Cross-sectional. 3545 subjects 6-19 yrs old who participated in the Hispanic Health and Nutrition Examination Survey. Pure tone audiometric evaluations were performed at 500 Hz, 2000 Hz, and 4000 Hz. Extensive measures on medical and sociodemographic covariates.	Blood Pb at the time of testing Blood Pb 50th percentile 8 µg/dL	Following covariate adjustment, higher blood Pb concentrations were associated with an increased risk of hearing thresholds that were elevated above the standard reference level at all four frequencies. Blood Pb was also associated higher hearing threshold when treated as a continuous outcome. These relationships extended to blood Pb levels below 10 µg/dL. An increase in blood Pb from 6 to 18 µg/dL was associated with a 2-dB loss at all frequencies. Authors conclude that HHANES results those reported earlier for NHANES-II.
Dietrich et al. (1992) U.S.	Design: Prospective/longitudinal. 215 subjects drawn from the Cincinnati Pb Study at the age of 5 yrs. Children were administered the SCAN-a standardized test of central auditory processing. Extensive measurement of medical and sociodemographic covariates	Prenatal (maternal) and serial postnatal blood Pb assessments Prenatal blood Pb 8.3 (SD 3.7) µg/dL Blood Pb at 2 yrs 17.4 (SD 8.8) µg/dL	Higher prenatal (maternal), neonatal and postnatal blood Pb concentrations were associated with more incorrect identification of common monosyllabic words presented under conditions of muffling. Following covariate adjustment, avg childhood blood Pb level remained significantly associated with impaired performance on the SCAN subtest. Authors conclude that Pb-related deficits in hearing and auditory processing may be one plausible mechanism by which an increased Pb burden might impede a child's learning.
Europe			
Osman et al. (1999) Poland	Design: Cross-sectional. 155 children 4-14 yr-old living in an industrial region of Poland. Pure tone audiometric evaluations were performed at 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, 6000Hz, and 8000 Hz. Basic data on medical history, limited information on sociodemographic covariates such as family structure and income.	Blood Pb at the time of testing Blood Pb median 7.2 (range 1.9-28) µg/dL	Higher blood Pb concentrations were significantly associated with increased hearing thresholds at all frequencies studied. This relationship remained significant when analyses were limited to subjects with blood Pb levels below 10 µg/dL. Authors conclude that auditory function in children is impaired at blood Pb concentrations below 10 µg/dL.

Table AX6-2.8. Effects of Lead on Neuromotor Function in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
United States			
Dietrich et al. (1993b); Bhattacharya et al. (1995); Ris et al. (2004) U.S.	Design: Prospective longitudinal. Relationship between Pb exposure and neuromotor function has been examined in several studies on the Cincinnati Pb Study Cohort from 6 to 17 yrs of age. At 6 yrs of age 245 subjects were administered the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP); at 610 yrs of age subjects were assessed for postural instability using a microprocessor-based strain gauge platform system and at 16-17 yrs of age the fine-motor skills of study subjects were assessed with the grooved pegboard and finger tapping tasks (part of a comprehensive neuropsychological battery). Extensive measurement of medical and sociodemographic factors.	Prenatal (maternal) and serial postnatal blood Pb assessments Prenatal blood Pb 8.3 (SD 3.7) µg/dL Blood Pb at 2 yrs 17.4 (SD 8.8) µg/dL	Following covariate adjustment, postnatal Pb exposure was significantly associated with poorer scores on BOTMP measures of bilateral coordination, visual-motor control, upper-limb speed and dexterity and the Fine Motor Composite score. Low-level neonatal blood Pb concentrations were also significantly associated with poorer scores on the aforementioned subtests, as well as measures of visual-motor control. Postnatal Pb exposure was significantly associated with greater postural instability in 610 yr-old subjects and poorer fine-motor coordination when examined at 16-17 yrs. Authors conclude that effects of early Pb exposure extend into a number of dimensions of neuromotor development.
Europe			
Wasserman et al. (2000a) Yugoslavia	Design: Prospective longitudinal. Birth cohort of ~300-400 infants followed since birth residing in two towns in Kosovo, Yugoslavia, one group near a longstanding Pb smelter and battery manufacturing facility and another in a relatively unexposed location 25 miles away. 283 children at age 54 mos were administered the Beery Developmental Test of Visual-Motor Integration (VMI) and the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP). Extensive measurement of medical and sociodemographic factors.	Maternal prenatal, umbilical cord and serial postnatal blood Pb Maternal blood Pb in exposed area 19.9 (SD 7.7) µg/dL, unexposed area 5.6 (SD 2.0) µg/dL Umbilical cord blood Pb in exposed area 22.2 (SD 8.1) µg/dL, unexposed area 5.5 (SD 3.3) µg/dL Blood Pb at 2 yrs in exposed area 35.4 µg/dL, unexposed area 8.5 µg/dL	Following covariate-adjustment, the log avg of serial blood Pb assessments to 54 mos was associated with lower Fine Motor Composite and VMI scores. Pb exposure was unrelated to gross motor performance. With covariate adjustment, an increase in avg blood Pb from 10 to 20 µg/dL was associated with a loss of 0.62 and 0.42 points respectively, in Fine Motor Composite and VMI. Authors noted that other factors such as indicators of greater stimulation in the home make a larger contribution to motor development than Pb.

Table AX6-2.9. Effects of Lead on Direct Measures of Brain Anatomical Development in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
United States			
Trope et al. (1998) U.S.	Design: Case-control. One 10 yr-old subject with history of Pb poisoning and unexposed 9 yr-old cousin. Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) were used to assess differences in cortical structures and evidence of neuronal loss. This was the first study to attempt to determine in vivo structural and/or metabolic differences in the brain of a child exposed to Pb compared with a healthy control.	Blood Pb Pb poisoned case 51 µg/dL at 38 mo Unexposed control not reported.	Both children presented with normal volumetric MRI. MRS revealed a significant alteration in brain metabolites, with a reduction in N-acetylaspartate:creatine ratio for both gray and white matter compared to the subject's cousin. Authors conclude that results suggest neuronal loss related to earlier Pb exposure.
Trope et al. (2001) U.S.	Design: Case-control. 16 subjects with a history of elevated blood Pb levels before 5 yrs of age and 5 age-matched siblings or cousins were evaluated. Avg age at time of evaluation was 8 yrs. Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) were used to assess differences in cortical structures and evidence of neuronal loss.	Blood Pb Range in Pb-exposed 23 to 65 µg/dL Controls <10 µg/dL	All children had normal MRI examinations, but Pb-exposed subjects exhibited a significant reduction in N-acetylaspartate:creatine and pohosphocreatine ratios in frontal gray matter compared to controls. Authors conclude that Pb has an effect on brain metabolites in cortical gray matter suggestive of neuronal loss.
Cecil et al. (2005) U.S.	Design: Prospective/longitudinal. 48 young adults ages 20 to 23 yrs were re-examined. Functional MRI (fMRI) was used to examine the influence of childhood Pb exposure on language function. Subjects performed a verb generation/finger-tapping paradigm. Extensive measurement of medical and sociodemographic covariates	Blood Pb Avg childhood blood Pb 13.9 (SD 6.6, range 4.8-31.1) µg/dL	Higher avg childhood blood Pb levels was significantly associated with reduced activation in Broca's area in the left hemisphere and increased activation in the right temporal lobe, the homologue of Wernicke'a area in the left hemisphere. Authors conclude that elevated childhood Pb exposure strongly influences neural substrates of semantic language function on normal language areas with concomitant recruitment of contra-lateral regions resulting in a striking dose-dependent atypical organization of language function.
Latin America			
Rothenberg et al. (2000) Mexico	Design: Prospective/longitudinal. 113 5-7 yr-old children from the Mexico City Prospective Study were re-examined. Brain stem auditory evoked potentials were recorded to assess the impact of prenatal and postnatal Pb exposure on development of auditory pathways. Results adjusted for gender and head circumference.	Blood Pb Prenatal (20 wks) 8.1 (SD 4.1) µg/dL Cord 8.7 (SD 4.3) µg/dL Postnatal 18 mo 10.8 (SD 5.2) µg/dL	Prenatal blood Pb at 20 wks was associated with decreased interpeak intervals. After fitting a nonlinear model to these data, I-V and III-V interpeak intervals decreased as blood Pb rose from 1 to 8 µg/dL and increased as blood Pb rose from 8 to 30 µg/dL. Increased blood Pb at 12 and 48 mos was related to decreased conduction intervals for I-V and II-V across the entire blood Pb range suggesting pathway length effects.
Asia			

Table AX6-2.9. Effects of Lead on Direct Measures of Brain Anatomical Development in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
Meng et al. (2005) China	Design: Case-control. 6 subjects with blood Pb concentrations □27 µg/dL and 6 controls with blood Pb concentrations <10 µg/dL were evaluated with Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy to evaluate structural abnormalities and differences in N-acetylaspartate, creatine, and choline in frontal lobes and hippocampus of cases and controls.	Blood Pb Cases 37.7 (SD 5.7) µg/dL Controls 5.4 (SD 1.5) µg/dL	All children presented with normal MRI. Peak values of N-acetylaspartate, choline, and creatine in all four brain regions were reduced in Pb exposed children relative to controls. Authors conclude that reduced brain N-acetylaspartate in cases may be related to decreased neuronal density or loss. Reduced choline signal may indicate decreased cell membrane turnover or myelin alterations while lower creatine may indicate reduced neuronal cell viability.

Table AX6-2.10. Reversibility of Lead-Related Deficits in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
United States			
Ruff et al. (1993) U.S.	Design: Intervention study, non-randomized. 126 children with complete data age 13 to 87 mos and with blood Pb levels between 25 and 55 µg/dL were given chelation with ETDA and/or therapeutic iron where indicated. At baseline and follow-up, patients were evaluated with the Bayley Scales of Infant Development, Mental Development Index, or Stanford Binet Scales of Intelligence depending upon age.	Blood Pb at time of treatment Blood Pb 31.2 (SD 6.5) µg/dL	Without respect to treatment regimen, changes in performance on cognitive measures after 6 mos were significantly related to changes in blood Pb levels after control for confounding factors. Standardized scores on tests increased 1 point for every 3 µg/dL decrement in blood Pb.
Rogan et al. (2001); Dietrich et al. (2004) U.S.	Design: Double blind, placebo-controlled randomized clinical trial. The Treatment of Pb-Exposed Children (TLC) clinical trial of 780 children in 4 centers was designed to determine if children with moderately elevated blood Pb concentrations given succimer would have better neuropsychological outcomes than children given placebo. Children between 12 and 33 mos of age were evaluated 3 yrs following treatments and again at 7 and 7.5 yrs of age. A wide range of neurological, neuropsychological, and behavioral tests was administered. Assessment of potentially confounding factors included sociodemographics and parental IQ.	Blood Pb Baseline blood Pb 26 (SD 26.5) µg/dL in both drug and placebo groups	Succimer was effective in lowering blood Pb levels in subjects on active drug during the first 6 mos of the trial. However, after 1 yr differences in the blood Pb levels of succimer and placebo groups had virtually disappears. 3 yrs following treatment, no statistically significant differences between active drug and placebo groups were observed for IQ or other more focused neuropsychological and behavioral measures. When evaluated at 7 and 7.5 yrs of age, TLC could demonstrate no benefits of earlier treatment on an extensive battery of cognitive, neurological, behavioral and neuromotor endpoints. Authors conclude that the TLC regimen of chelation therapy is not associated with neurodevelopmental benefits in children with blood Pb levels between 20 and 44 µg/dL and that these results emphasize the importance of taking environmental measures to prevent exposure to Pb in light of the apparent irreversibility of Pb-associated neurodevelopmental deficits.
Liu et al. (2002)U.S.	Design: Prospective longitudinal clinical trial. Data from the Treatment of Pb-Exposed Children (TLC) used to examine prospective relationships between falling blood Pb levels and changes in cognitive functioning. 741 children recruited between 13 and 33 mos of age were assessed at baseline and 6 mos later with the Bayley Mental Development Index (MDI) and 36 mos post-randomization with the Wechsler Preschool and Primary Scales of Intelligence-Revised to obtain IQ.	Blood Pb Baseline blood Pb 26.2 (SD 5.1) µg/dL 36 mos post-randomization blood Pb 12.2 (SD 5.2) µg/dL	TLC found no overall effect of changing blood Pb level on change in cognitive test scores from baseline to 6 mos. Slope estimated to be 0.0 points per 10 µg/dL change in blood Pb. From baseline to 36 mos and 6 mos to 36 mos, falling blood Pb levels were significantly associated with increased cognitive test scores, but only because of an association in the placebo group. Authors conclude that because improvements were not observed in all children, the data do not provide support that Pb-induced cognitive impairments are reversible. Although the possible neurotoxicity of succimer cannot be ruled out.
Latin America			
Kordas et al. (2005); Rico et al. (2006)	Design: Double-blind, placebo-controlled nutritional supplementation clinical trial conducted	Blood Pb Baseline blood Pb 11.5	No significant effects of treatment on behavior or cognition could be detected with any consistency. Authors conclude that

Table AX6-2.10. Reversibility of Lead-Related Deficits in Children

Reference, Study Location, and Period	Study Description	Pb Measurement	Findings, Interpretation
Mexico	among 602 1st grade children ages 6-8 yrs in Torreón, Mexico. Subjects received iron, zinc, both or placebo for 6 mos. Parents and teachers filled out the Conners Rating Scales at baseline and follow-up six mos following the end of supplementation to index behavioral changes following therapy. In addition, 11 cognitive tests of memory, attention, visual-spatial abilities, and learning were administered, including WISCR-M at baseline and follow-up 6 mos later.	(SD 6.1) µg/dL	this regimen of supplementation does not result in improvements in ratings of behavior or cognitive performance.
Asia			
Tong et al. (1998) Australia	Design: Prospective longitudinal. 375 children from the Port Pirie Prospective Study were followed from birth to the age of 11-13 yrs. Bayley Mental Development Index (MDI) at 2 yrs, the McCarthy Scales General Cognitive Index (GCI) and IQs from the Wechsler Intelligence Scale served as the primary indicators of intellectual status. The purpose of the study was to assess the reversibility of Pb effects on cognition in relationship to declines in blood Pb over time.	Postnatal blood Pb Mean blood Pb at 2 yrs 21.2 µg/dL declining to 7.9 µg/dL at 11-13 yrs	Although blood Pb levels declined substantially, covariate adjusted scores on standardized measures of intellectual attainment administered at 2, 4, 7, and 11-13 yrs of age were unrelated to declining body burden. Authors conclude that effects of early exposure to Pb during childhood are not reversed by a subsequent decline in blood Pb concentration.

Appendix B. Developmental Effects of Lead in Experimental Animals (From the the October 2006 EPA Air Quality Criteria for Lead)

Table AX5-4.1. Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Al-Hakkak et al. (1988)	Mouse/BALB/c, weaning	0, 25, 50 mg Pb monoxide alloy/kg in chow for 35–70 days	Reduced number of spermatogenia and spermatocytes in the 50 mg group after 70 days; reduced number of implantations after mating (after 35 days exposure).	PbB not reported
Appleton (1991)	Rat/Long-Evans hooded, adult	Pb acetate single dose by i.v. at 30 mg/kg	Increase in serum calcium and phosphorous; SEM analysis revealed 'Pb line' in tooth that was composed of hypomineralized interglobular dentine.	PbB not reported
Bataineh et al. (1998)	Rat/Sprague Dawley, adult	1000 ppm Pb acetate in drinking water for 12 wks	Fertility was reduced; total number of resorptions was increased in female rats impregnated by males.	PbB not reported
Berry et al. (2002)	Rat/Sprague-Dawley, 21 days old	Pb nitrate (1000 ppm Pb) in drinking water for 6 wks	Mean plasma growth hormone levels decreased by 44.6%; reduced mean growth hormone amplitude by 37.5%, mean nadir concentration by 60%, and growth hormone peak area by 35%; findings are consistent with decreased hypothalamic growth hormone-releasing factor secretion or reduced somatotrope responsiveness; exogenous growth hormone in Pb-treated and control rats, this response was blunted by the Pb treatment; plasma IGF1 concentration was not significantly affected by Pb treatment.	PbB 37.40 ± 3.60 µg/dL
Bogden et al. (1995)	Rat/Sprague Dawley, 12 wks old	250 mg/L of Pb acetate in drinking water from GD 1 until after 1 wk after weaning	Dam and pup hemoglobin concentrations, hematocrit, and body weights and lengths were reduced.	PbB <15 µg/dL
Camoratto et al. (1993)	Rat/Sprague Dawley, adult	0.02% Pb nitrate in drinking water from gestation day 5 of dams until PND 4 of offspring	Female pups exposed to Pb beginning in utero were smaller, no corresponding effect in males; pituitary responsiveness to a hypothalamic stimulus.	PbB 17–43 µg/dL
Corpas (2002a)	Rat/Wistar, adult	Pb acetate 0 or 300 mg/L in drinking water during gestation and lactation	Alterations in hepatic system of neonates (PND 12) and pups (PND 21); reductions in hemoglobin, iron, alkaline and acid phosphatase levels, and hepatic glycogen, and elevated blood glucose.	PbB ~22 µg/dL
Corpas (2002b)	Rat/Albino (NOS), adult	Pb acetate 0 or 300 mg/L in drinking water during gestation and lactation	Effects energy metabolism; decrease in testis and seminal vesicle weights, and an increase in DNA and RNA levels on PN day 21; protein was significantly decreased, alkaline and acid phosphatase levels of the gonads were reduced; reduction of the thickness of the epithelium and seminiferous tubule diameter.	PbB 54–143 µg/dL
Cory-Slechta et al. (2004)†	Rat/Long-Evans, adult	Pb acetate in drinking water (150 ppm); 2 mo before breeding until the end of lactation 14 rats no maternal stress Pb exposure, 15 rats no maternal stress with Pb exposure, 18 rats maternal stress without Pb exposure, 23 rats maternal stress and Pb exposure	Pb alone (in male) ($p < 0.05$) and Pb plus stress (in females) ($p < 0.05$) permanently elevated corticosterene levels in offspring.	PbB 30–40 µg/dL
Dey et al. (2001)	Mouse/Albino (NOS), ~100 g	Pb citrate 5 µg/kg-d p.o. from early pregnancy (NOS) until birth	Perforations, tissue damage, cell deformity, disordered organization of collagen bundles found in offspring; reduction in the symmetry of sulphate group of skin pups of mice exposed to Pb citrate (5 µg/kg-d) throughout gestation exhibited a variety of skin anomalies, including perforations, tissue damage, cell deformity, and disordered collagen bundles Pb was found to affect initial genomic expression in embryos fathered by male rats.	PbB not reported

Table AX5-4.1. Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Flora and Tandon (1987)	Rat/Albino (NOS), adult	Pb nitrate dissolved in water 2– 20 mg/kg-d i.v. on day 9, 10, 11 of gestation; 6 rats in each group (0, 5, 10, 20, 40 mg/kg Pb)	Dose-dependant increase in external malformations at all doses ($p < 0.001$), particularly tail defects; dose dependant decrease in number of live births at 20 and 400 mg/kg ($p < 0.001$); dose-dependent increase in number of resorptions per dam at #10 mg/kg ($p < 0.01$).	PbB 13–45 µg/dL
Fox et al. (1991a)	Rat/Long-Evans hooded, adult	Lactation exposure via dams exposed to 0.02 or 0.2% Pb in drinking water from PND 1 through weaning (PND 21) 8 female pups per litter (number of litter unspecified) control pups, 8 pups for litter (number of litter unspecified) low level exposure pups, 8 pups per litter (number of litter unspecified) moderate level exposure pups	Long-term, dose-dependent decreases retinal Na/K ATPase activity in the female offspring (only female pups were used) (!11%; !26%) ($p < 0.05$).	PbB 18.8 or 59.4 µg/dL at weaning
Fox et al. (1997)†	Rat/Long-Evans hooded, adult	0.02 or 0.2% Pb acetate in drinking water from PND 0– PND 21; 8 female pups per litter control pups; 8 pups per litter low level exposure; 8 pups per litter moderate level exposure (number of litters per dose unspecified)	Developmental and adult Pb exposure for 6 wks produced age and dose-dependent retinal degeneration such that rods and bipolar cells were selectively lost; at the ultrastructural level, all dying cells exhibit the classical morphological features of apoptotic cell death; decrease in the number of rods was correlated with the loss of rhodopsin content per eye confirming that rods were directly affected by Pb ($p < 0.05$); single-flash rod ERGs and cone ERGs obtained from Pb-exposed rats demonstrated that there were age- and dose-dependent decreases in the rod a-wave and b-wave sensitivity and maximum amplitudes without any effect on cones; in adult rats exposed to Pb for 3 wks, qualitatively similar ERG changes occurred in the absence of cell loss or decrease in rhodopsin content ($p < 0.05$); developmental and adult Pb exposure for three and 6 wks produced age- and dose-dependent decreases in retinal cGMP phosphodiesterase (PDE) activity resulting in increased CGMP levels ($p < 0.05$); retinas of developing and adult rats exposed to Pb exhibit qualitatively similar rod mediated ERG alterations as well as rod and bipolar apoptotic cell death ($p < 0.05$); similar biochemical mechanism such as the inhibition of rod and bipolar cell cGMP PDE, varying only in degree and duration, underlies both the Pb-induced ERG rod-mediated deficits and the rod and bipolar apoptotic cell death ($p < 0.05$).	PbB weanlings 19 ± 3 (low exposure) or 59 ± 8 µg/dL (moderate exposure), adult 7 ± 2 µg/dL (at PND 90)
Gandley et al. (1999)	Rat/Sprague-Dawley, adult	Male rats exposed to 25 or 250 ppm acetate Pb in drinking water for at least 35 days prior to breeding	Fertility was reduced in males with PbB in range 27–60 µg/dL, Pb was found to affect initial genomic expression in embryos fathered by male rats with blood Pb levels as low as 15–23 µg/dL; dose-dependant increases were seen in an unidentified set of proteins with a relative molecular weight of ~70 kDa.	PbB 27–60 µg/dL (fathers) 15–23 µg/dL (offspring)
Govoni et al. (1984)	Rat/Sprague-Dawley, adult	2.5 mg/mL Pb acetate in drinking water from GD 16 to postnatal week 8	Decreased sulpiride binding in the pituitary is consistent with the elevated serum PRL concentrations previously described in Pb-exposed rats; DOPAc concentrations were reduced by 21% in Pb-treated rats.	PbB 71 ± 8 µg/dL

Table AX5-4.1. Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Hamilton et al. (1994)	Rat/Sprague-Dawley, 25 days old	Pb acetate in drinking water at 250, 500 or 1000 ppm; 8 wks prior to mating through GD 21	Altered growth rates; reduced early postnatal growth; decreased fetal body weight.	PbB 40–100 µg/dL
Han et al. (2000)	Rat/Sprague-Dawley, 5 wks old	250 mg/mL Pb acetate in drinking water for 5 wks followed by 4 wks no exposure (mated at end of 4-wk no exposure period)	Pups born to Pb-exposed dams had significantly ($p < 0.0001$) lower mean birth weights and birth lengths.	PbB 10–70 µg/dL
Hanna et al. (1997)	Mouse/Swiss ICR preimplantation embryos	In vitro incubation of two- and four-cell embryos with 0.05– 200 µM Pb acetate for 72 hr (time required for blastocyst formation)	Exposure of embryos to Pb was only toxic at 200 µM, which reduced cell proliferation and blastocyst formation.	PbB not reported
Iavicoli et al. (2003)	Mouse/Swiss, adult	Pb acetate in food (0.02, 0.06, 0.11, 0.2, 2, 4, 20, 40 ppm) exposure began 1 day after mating until litter was 90 days old one litter of mice exposed to each dietary concentration	Low-level exposure (PbB 2–13 µg/dL) reduced red cell synthesis ($p < 0.05$); high-level exposure (PbB 0.6–2 µg/dL) enhanced red cell synthesis ($p < 0.05$).	PbB 0.6 to <2.0 µg/dL or >2.0–13 µg/dL
Iavicoli et al. (2004)	Mouse/Swiss, adult	Pb acetate in feed; exposure began 1 day after mating until litter was 90 days old	In females: accelerated time to puberty at PbB <3 µg/dL; delayed time to puberty at 3–13 µg/dL.	PbB 0.6 to <2.0 µg/dL or >2.0–13 µg/dL
Lögdberg et al. (1987)	Monkey/ Squirrel, adult	Pb acetate p.o. exposure of gravid squirrel monkeys from week 9 of gestation through PND 0	Increase in pre- and perinatal mortality among squirrel monkeys receiving Pb acetate p.o. during the last two-thirds of pregnancy (45% vs. 7–8% among controls); mean maternal PbB was 54 µg/dL (39–82 µg/dL); statistically significant reductions in mean birth weight were observed in Pb-exposed monkeys as compared to controls; effects occurred without clinical manifestation of toxic effects in the mothers.	PbB 54 µg/dL (39–82 µg/dL)
Lögdberg et al. (1998)	Monkey/ Squirrel, adult	Pb acetate (varying concentrations ≤0.1% in diet); maternal dosing from 5–8.5 wks pregnant to PND 1; 11 control monkeys, 3 low-Pb exposure group (PbB24 µg/dL), 7 medium Pb group(PbB 40 µg/dL, 5 high-Pb group (PbB 56 µg/dL)	Dose-dependent reduction in placental weight ($p < 0.0007$); various pathological lesions were seen in the placentas ($n = 4$), including hemorrhages, hyalinization of the parenchyma with destruction of the villi and massive vacuolization of chorion epithelium; effects occurred without clinical manifestation of toxic effects in the mothers.	Mean maternal PbB 37 µg/dL (22–82 µg/dL 24 (22–26) µg/dL (low dose) 40 (35–46) µg/dL (mid dose) 56 (43–82) µg/dL (high dose)
McGivern et al. (1991)†	Rat/Sprague-Dawley, adult	0.1% Pb acetate in drinking water from GD 14 to parturition	Male offspring of dams exhibited reduced sperm counts, altered male reproductive behavior, and enlarged prostates later in life; females exhibited delayed puberty, menstrual irregularities, and an absence of observable corpora lutea; males and females exhibited irregular release patterns of both FSH and LH later in life.	PbB 73 µg/dL
Nayak et al. (1989a)	Mouse/Swiss Webster, adult	Pb nitrate dissolved in NaCl solution, administered intravenously, via caudal vein at dose levels of 100, 150, 200	Chemical analysis showed Pb was readily transferred across placenta; Pb caused moderate, statistically significant, increase in frequency of SCEs in maternal bone marrow cells and significant reduction in NORs at the 2 highest dose levels (150 and200 mg/kg); animals showed	PbB levels at birth in the exposure groups for these studies were >180

Table AX5-4.1. Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
		mg/kg; one time exposure on GD 9	several specific chromosomal aberrations, mostly deletions, in maternal bone, marrow, and fetal cells; aneupoidy was found to be frequently associated with the lowest dose levels of Pb nitrate (100 mg/kg); increased embryonic resorption and reduced placental weights.	µg/dL
Piasek and Kostial (1991)	Rat/Wistar, 10 wks old	7500 ppm Pb acetate in drinking water for 9 wks	Decrease in litter size, pup survival, and birth weight; food consumption, body weight, and fertility were not altered in 20 wk exposure period.	Maternal PbB >300 µg/dL Offspring PbB >220 µg/dL
Pinon-Lataillade et al. (1995)	Mouse/NMRI, adult	0–0.5% Pb acetate in drinking water exposed to Pb during gestation until post-GD 60	Pb exposure during gestation reduces litter size; reduced birth weight and growth rates.	PbB <4–132 µg/dL
Pillai and Gupta (2005)	Rat/Charles Foster, 200–220 g	Subcutaneous injection of 0.05 mg/kg-d Pb acetate for 5–7 days prior to mating through PND 21	Long term exposure of rats (premating, gestational, and lactational) to moderate levels of Pb acetate (s.c.) resulted in reduced activities of hepatic steroid (E2) metabolizing enzymes (17-ß-hydroxy steroid oxidoreductase and UDP glucuronyl transferase) and decreased hepatic CYP450 content.	PbB not reported
Ronis et al. (1996)†	Rat/Sprague-Dawley, 22, 55 days or plug-positive time-impregnated	0.6% Pb acetate in drinking water for various durations: PND 24–74 (pubertal exposure), PND 60–74 (post pubertal exposure); 11 males and females in pubertal exposure group (10 each in control pubertal group); 6 males and females postpubertal exposure and control groups	Reduction in serum testosterone levels in male, not female; in female suppression of circulating E2 ($p < 0.05$) and LH ($p < 0.05$); reduction in male secondary sex organ weight ($p < 0.0005$); delayed vaginal opening and disrupted diestrous in females ($p < 0.005$); increased incidence of stillbirth (2% control vs. 19% Pb) ($p < 0.005$).	In utero PbB 250–300 µg/dL Pre-pubertal PbB 30–60 µg/dL Post-pubertal PbB 30–60 µg/dL PbBs in the dams and offspring in this experiment were >200 µg/dL.
Ronis et al. (1998a)†	Rat/Sprague-Dawley, various ages	0.6% Pb acetate in drinking water ad libitum for various durations: GD 5 to PND 1, GD 5 to weaning, PND 1 to weaning 3 control litters, 2 gestation exposure litters, 2 lactation exposure litters, 2 gestation and lactation exposure litters, 2 postnatal litters, 2 chronic litters (4 male and 4 female pups per litter)	Dose-dependent delay in sexual maturation (delayed vaginal opening) ($p < 0.0002$) following prenatal Pb exposure that continued until adulthood (85 days old); reduced birth weight ($p < 0.05$), more pronounced among male pups.	Group: pup PbB Naïve: ~6 µg/dL Control: <2 µg/dL Gest: ~10 µg/dL Lact: ~3 µg/dL Gest+Lact: ~13 µg/dL Postnatal: ~260 µg/dL Chronic: ~287 µg/dL

Table AX5-4.1. Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Ronis et al. (1998b)†	Rat/Sprague-Dawley, adult	Pb acetate in drinking water (0.05% to 0.45% w/v); dams exposed until weaning, exposure of pups which continued until PND 21, 35, 55, or 85; 5 control litters (0%), 10 low-dose litters (0.05%), 8 mid-dose litters (0.15%), 9 high-dose litters (0.45%); 4 male and 4 female pups per litter	Prenatal Pb exposure that continues until adulthood (85 days old) delays sexual maturation in female pups in a dose-related manner ($p < 0.05$); birth weight reduced ($p < 0.05$), more pronounced among male pups; decreased growth rates ($p < 0.05$) in both sexes accompanied by decrease in plasma concentrations of IGF1 through puberty ($p < 0.05$) and a significant increase in pituitary and growth hormone during puberty ($p < 0.05$).	PbBs in the pups between the ages of 21 and 85 days were >100 µg/dL and reached up to 388 µg/dL.
Ronis et al. (1998c)	Rat/Sprague-Dawley, adult	Pb acetate 0.05, 0.15, or 0.45% in drinking water beginning GD 5 continuing until PND 21, 35, 55, or 85; 5 control litters (0%), 10 low-dose litters (0.05%), 8 mid-dose litters (0.15%), 9 high-dose litters (0.45%); 4 male and 4 female pups per litter	Dose-responsive decrease in birth weight ($p < 0.05$), and crown-to-rump length ($p < 0.05$); dose-responsive delay in sexual maturity in male ($p < 0.05$) and female ($p < 0.05$); neonatal decrease in sex steroids ($p < 0.05$); pubertal decrease in testosterone (male) ($p < 0.05$) and E2 (female) ($p < 0.05$); decrease estrous cyclicity at high dose ($p < 0.05$).	Dams: 0, 48, 88, or 181 µg/dL Pups PND 1: <1, ~40, ~70, or >120 µg/dL Pups PND 21: <1, >50, >160, or ~237 µg/dL Pups PND 35: <1, ~22, >70, or >278 µg/dL Pups PND 55: <1, >68, >137, or ~380 µg/dL Pups PND 85: <1, >43, >122, or >214 µg/dL
Ronis et al. (2001)†	Rat/Sprague-Dawley, neonate, male (100 days) and female pup	Pb acetate in drinking water to 825 or 2475 ppm ad libitum from G'D 4 to GD 55 postpartum; 1 male and female pup/litter (5 litters per group) control group, 1 male and female pup/litter (5 litters per group) 825 ppm Pb acetate group, 1 male and female pup/litter (5 litters per group) 2475 ppm Pb acetate group	Dose-dependent decrease of the load of failure in male ($p < 0.05$); no difference in plasma levels of vitamin D metabolites; reduced somatic growth ($p < 0.05$), longitudinal bone growth ($p < 0.05$), and bone strength during the pubertal period ($p < 0.05$); sex steroid replacement did not restore skeletal parameters in Pb exposed rats; L-Dopa increased plasma IGF_1 concentrations, rates of bone growth, and bone strength measures in controls while having no effect in Pb exposed groups; DO gap x-ray density and proximal new endostreal bone formation were decreased in the distration gaps of the Pb-treated animals ($p < 0.01$); distraction initiated at 0.2 mm 30 to 60 days of age.	PbB at 825 ppm was 67– 192 µg/dL PbB at 2475 ppm was 120– 388 µg/dL
Sant'Ana et al. (2001)	Rat/Wistar, 90 days old	0.1 and 1% Pb in drinking water 7 days	1% Pb exposure reduced offspring body weight during treatment, no changes observed after 0.1% exposure; no altered offspring sexual maturation, higher Pb improved sexual behavior, while 0.1% reduced it; 0.1% Pb caused decrease in testis weight, an increase in seminal vesicle weight, and no changes in plasma testosterone levels, hypothalamic VMA levels were increased compared to control group; reduced birth weight and growth rates.	PbB 36.12 — 9.49 µg/dL or 13.08 ± 9.42 µg/dL

Table AX5-4.1. Effect of Lead on Reproduction and Development in Mammals Effects on Offspring

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Singh et al. (1993b)	Rat/ITRC, albino (NOS), 6 wks old	250, 500, 1000, and 2000 ppm Pb nitrate in drinking water from GD 6 to GD 14	Significantly reduced litter size, reduced fetal weight, and a reduced crown-to-rump length, increased resorption and a higher blood-Pb uptake in those groups receiving 1000 and 2000 ppm Pb; these also had a higher placental uptake; however the level was the same in both groups; fetal Pb uptake remained the same whether or not 2000 ppm Pb was given to an iron-deficient or normal iron groups of mothers.	PbB not reported
Watson et al. (1997)	Rat/Sprague-Dawley, adult	Pb in drinking water at 34 ppm from weaning of mothers through gestation and weaning of offspring until birth; 6 pups control group, 6 pups experimental group	Reduced body weight ($p = 0.04$); parotid function was decreased by nearly 30% ($p = 0.30$); higher mean caries scores than the control pups ($p = 0.005$); pre- and perinatal Pb exposure had significantly increased susceptibility to dental caries ($p = 0.015$).	PbB 48 ± 13 µg/dL
Wiebe et al. (1998)	Rats/Sprague-Dawley, adult	20 or 200 ppm Pb chloride in drinking water; prior to pregnancy, during pregnancy, lactation	Exposure to Pb did not affect tissue weights but did cause a significant decrease in gonadotropin-receptor binding in the prepubertal, pubertal, and adult females; conversion of progesterone to androstenedione and dihydrotestosterone was significantly decreased in 21-day old rats, in 150-day old females, the exposure to Pb resulted in significantly increased conversion to the 5-alpha-reduced steroids, normally high during puberty.	PbB 4.0 ± 1.4 to 6.6 ± 2.3 µg/dL

*Not including effects on the nervous or immune systems.

† Candidate key study.

cGMP, cyclic guanosine—3',5'-monophosphate; DO, distraction osteogenesis; DOPAc, 3,4-dihydroxyphenylacetic acid; E2, estradiol; ERG, electroretinographic; FSH, follicle stimulating hormone; GD, gestational day; IGF1, insulin-like growth factor 1; i.v., intravenous; kDA, kilodalton; LH, luteinizing hormone; NOS, not otherwise specified; PbB, blood Pb concentration; PDE, phosphodiesterase; PND, post-natal day; p.o., per os (oral administration); s.c., subcutaneous; SEM, standard error mean; UDP, uridine diphosphate; VMA, vanilmandelic acid

Appendix C. Male Reproductive Effects of Lead in Humans
(From the October 2006 EPA Air Quality Criteria for Lead)

Table AX6-6.2. Lead Exposure and Male Reproduction: Semen Quality

Reference and Study Location	Study Description	Pb Measurement	Findings, Interpretation
United States			
Benoff et al. (2003a) New York	74 male partners of women undergoing their first in vitro fertilization cycle.	Seminal plasma Pb: Mean 39.50 µg/dL (SD 35.97)	Significant negative correlation between seminal plasma Pb and fertilization rate (r = !0.447). Statistically significant inverse correlations (r values of <!0.3) were found between seminal plasma Pb levels and sperm count, motility, and morphology. Stronger negative relationships were observed between seminal plasma Pb values and mannose receptor expression (r = !0.383), and mannose-stimulated acrosome loss (r = !0.423).
Benoff et al. (2003b) New York	15 semen donors in an artificial insemination program. None were occupationally exposed to Pb.	Seminal plasma Pb: Range <10 to >150 µg/dL	Correlation coefficient for seminal plasma Pb and artificial fecundity rate is !0.641.
Cullen et al. (1984) U.S.	Seven men with symptomatic occupational Pb intoxication.	Maximum whole blood Pb levels: 66-139 µg/dL	Although serum testosterone concentration was normal in six patients, five had defects in spermatogenesis, including two with oligospermia and two with azoospermia. Repeat examinations after chelation therapy showed only partial improvement. Heavy occupational exposure to Pb may be associated with diffuse disturbances of endocrine and reproductive functions in men that are not rapidly reversible with standard treatment.
Canada			
Alexander et al. (1996a) British Columbia	119 workers employed at a Pb smelter.	Current blood Pb: Mean 22.4 µg/dL (range 5-58)	Sperm concentration and total sperm count were inversely related to current blood Pb concentration, with the largest effects detected among men with blood Pb concentrations of 40 µg/dL or more. Blood Pb (µg/dL) — Geometric mean sperm count ($x10^6$) <15 — 186.0 15-24 — 153.0 12-39 — 137.0 > 40 — 89.1 Blood Pb levels were not consistently associated with abnormal morphology and poor motility of the sperm. When classified by long term exposure to Pb, calculated from the mean blood Pb concentrations of the preceding 10 yrs, similar trends were observed.
Europe			
Bonde et al. (2002) UK, Belgium, Italy	European study of 503 men (362 exposed to Pb, 141 unexposed controls) employed in Pb industry.	Blood Pb: Exposed workers: Mean 31.0 µg/dL (range 4.6-	Median sperm concentration reduced by 49% in men with blood Pb levels >50 µg/dL.

Table AX6-6.2. Lead Exposure and Male Reproduction: Semen Quality

Reference and Study Location	Study Description	Pb Measurement	Findings, Interpretation
		64.5) Unexposed workers: Mean 4.4 µg/dL	Odds ratio for sperm count #50 million/ml in men with blood Pb levels >50 µg/dL compared to <10 µg/dL was 4.4 (95% CI: 1.6, 11.6). Regression analyses indicated a threshold value of 44 µg/dL below which no adverse associations were found.
Assennato et al. (1986) Italy	18 battery workers (exposed group) and 18 cement workers (control group).	Blood Pb: Battery workers: Mean 61 µg/dL (SD 20) Cement workers: Mean 18 µg/dL (SD 5) Semen Pb: Battery workers: Mean 79 µg/dL (SD 36) Cement workers: Mean 22 µg/dL (SD 9)	Sperm count and blood Pb: r_2 = !0.385 Sperm count and sperm Pb: r_2 = !0.026 38% lower median sperm count and threefold greater prevalence of oligospermia (16.7% vs. 5.5%) in battery workers compared to cement workers.
Lancranjan et al. (1975) Europe	150 men occupationally exposed to Pb divided into four groups: Pb-poisoned workmen (n = 23) and those showing a moderate (n = 42), slight (n = 35), or physiologic absorption (n = 50).	Blood Pb: Pb poisoned workers: Mean 74.5 µg/dL Moderately exposed workers: Mean 52.8 µg/dL	Decreased sperm counts and increased prevalence of morphologically abnormal sperm amongst workers with heavy and moderate exposure to Pb.
Latin America			
Hernandez-Ochoa et al. (2005) Region Lagunera, Mexico	68 environmentally-exposed men residing in Torreón, Gómez Palacio, and Lerdo for at least 3 yrs.	Blood Pb: Geometric mean 9.3 µg/dL (range 2-24) Seminal fluid Pb: Geometric mean 2.02 µg/L (range 1.14-12.4) Pb in spermatozoa: Geometric mean 0.047 ng/10_6 cells (range 0.0320.245)	Decreased sperm concentration, motility, normal morphology and viability correlated with Pb in spermatozoa. Reduced semen volume associated with seminal fluid Pb. Multiple linear regression indicated that percentages of progressive motility and morphology were the most sensitive parameters to Pb toxicity, which showed the highest percentages of abnormality among the semen quality parameters evaluated. No associations were found with blood Pb.
Lerda (1992) Argentina	38 male workers exposed to Pb in a battery factory and 30 controls.	Blood Pb: A (n = 12): mean 86.6 µg/dL (SD 0.6) B (n = 11): mean 65.9 µg/dL (SD 1.6)	Decreased sperm count, decreased percent motility, and increased percent with abnormal morphology observed in all three exposure groups compared to control group.

Table AX6-6.2. Lead Exposure and Male Reproduction: Semen Quality

Reference and Study Location	Study Description	Pb Measurement	Findings, Interpretation
		C (n = 15): mean 48.6 µg/dL (SD 4.2) Controls (n = 30): mean 23.5 µg/dL (SD 1.4)	
Asia			
Chowdhury et al. (1986) India	Ten men occupationally exposed to Pb in a printing press.	Blood Pb: Exposed group: Mean 42.5 µg/dL Unexposed group: Mean 14.8 µg/dL	Decrease in sperm count, percent motility and increase in number of sperm with abnormal morphology observed in these semen samples.

Table AX6-6.3. Lead Exposure and Male Reproduction: Time to Pregnancy

Reference and Study Location	Study Description	Pb Measurement	Findings, Interpretation
Europe			
Joffe et al. (2003) Belgium, England, Finland, Italy	Asclepios Project, large European collaborative cross-sectional study. 1,108 men (638 occupationally exposed to Pb at the time of pregnancy) who have fathered a child.	Blood Pb: Belgium: mean 31.7 µg/dL England: mean 37.2 µg/dL Finland: mean 29.3 µg/dL Italy: mean 29.2 µg/dL	Blood Pb (µg/dL) — Fecundity density ratios (95% CI) control — 1.00 <20 — 1.12 (0.84, 1.49) 20-29 — 0.96 (0.77, 1.19) 30-39 — 0.88 (0.70, 1.10) >40 — 0.93 (0.76, 1.15) Results indicate that no association was found between blood Pb and delayed time to pregnancy. Similar results were found when duration of exposure or cumulative exposure was used as the exposure metric.
Apostoli et al. (2000) Italy	Italian men included in the Asclepios project. 251 exposed men and 45 unexposed men with at least one completed pregnancy.	Blood Pb distribution among exposed men: Blood Pb (µg/dL) — % of population 0-19 — 14% 20-29 — 40% 30-39 — 32% > 40 — 40%	Among the exposed men, a longer time to pregnancy observed with blood Pb levels >40 µg/dL, though not statistically significant.
Sallmen et al. (2000a) Finland	502 occupationally exposed males monitored by the Finnish Institute of Occupational Health.	Blood Pb distribution (available close to time of conception in 62% of men; in 38% estimated based on blood Pb levels obtained at other times or based on job histories): Blood Pb (µg/dL) — % of population < 10 — 35% 10-20 — 40% 21-30 — 16% 31-39 — 4% > 40 — 5%	Results suggest that paternal exposure to Pb may be associated with increased time to pregnancy. Blood Pb (µg/dL) — Fecundity density ratios (95% CI) <10 — 1.00 10-20 — 0.92 (0.73, 1.16) 21-30 — 0.89 (0.66, 1.20) 31-39 — 0.58 (0.33, 0.96) >40 — 0.83 (0.50, 1.32)
Asia			
Shiau, et al. (2004) Taiwan	280 pregnancies in 133 couples in which male partner employed in battery plant. 127 conceived during exposure; remainder conceived prior to exposure.	Blood Pb: Annual means from 1987 to 1999 ranged from 32 to 41 µg/dL.	Blood Pb (µg/dL) — Fecundity density ratios (95% CI) unexposed — 1.00 <20 — 0.91 (0.61, 1.35) 20-29 — 0.71 (0.46, 1.09) 30-39 — 0.50 (0.34, 0.74) >40 — 0.38 (0.26, 0.56) Blood Pb: Annual means from 1987 to 1999 ranged from 32 to 41 µg/dL.

Table AX6-6.4. Lead Exposure and Male Reproduction: Reproductive History

Reference and Study Location	Study Description	Pb Measurement	Findings, Interpretation
United States			
Lin et al. (1996) New York	4,256 male workers reported to the New York State Heavy Metals Registry (exposed) and 5,148 male bus drivers from the New York State Department of Motor Vehicles file (control), frequency-matched for age and residence. Fertility during the period of 1981 to 1992. Records linked to birth certificates from the New York State Office of Vital Statistics.	Blood Pb in Pb-exposed men: Mean 37.2 µg/dL (SD 11.1)	Standardized fertility ratio of Pb-exposed men in comparison with non-exposed men was 0.88 (95% CI: 0.81, 0.95). Exposed group had fewer births than expected. Among those employed in Pb industry over 5 yrs, a relative risk of 0.38 (95% CI: 0.23, 0.61) was observed after adjusting for age, race, education, and residence.
Europe			
Gennart et al. (1992) Belgium	74 men occupationally exposed to Pb for more than 1 yr and 138 men in reference group with no occupational exposure.	Blood Pb in Pb-exposed men: Mean 40.3 µg/dL Duration of Pb exposure: Mean 10.7 yrs	Compared to reference group, odds of at least one live birth reduced in exposed group during the period of Pb exposure (odds ratio of 0.65 [95% CI: 0.43, 0.98]). Fertility decreased with increasing exposure (although number of men at higher exposure levels small).
Bonde and Kolstad (1997) Denmark	1,349 male employees ages 20-49 yrs from three battery plants and control group of 9,656 men not employed in Pb industry. Cohorts identified by records in a national pension fund. Information on births obtained from Danish Population Register.	Blood Pb in subset of battery worker cohort (4,639 blood samples from 400 workers): Mean 35.9 µg/dL (SD 13.0)	No associations found between exposure measure and birth rate. Relative risk comparing person yrs at risk from Pb exposure with yrs at risk in reference group was 0.88 (95% CI: 0.81, 0.95).
Sallmen et al. (2000b) Finland	Occupationally exposed males monitored by the Finnish Institute of Occupational Health. 2,111 individuals with probable exposure (a blood Pb level >10 µg/dL within a 5-yr time period including a calendar yr preceding the yr of marriage and 4 consecutive yrs) and 681 controls (with mean blood Pb levels <10 µg/dL).	Blood Pb distribution among individuals probably exposed: Blood Pb (µg/dL) / % of population 10-20 / 51% 21-30 / 30% 31-40 / 11% 41-50 / 5% > 51 / 3%	Risk ratios among men in the probably exposed group: Blood Pb (µg/dL) / Infertility ratios (95% CI) controls / 1.00 10-20 / 1.27 (1.08, 1.51) 21-30 / 1.35 (1.12, 1.63) 31-40 / 1.37 (1.08, 1.72) 41-50 / 1.50 (1.08, 2.02) >51 / 1.90 (1.30, 2.59) Results suggest that paternal exposure to Pb increases the risk of infertility at low occupational exposure levels.

Appendix D. Reproductive Effects of Lead in Experimental Animals (From the October 2006 EPA Air Quality Criteria for Lead)

Table AX5-4.2. Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Acharya et al. (2003)	Mouse/Swiss, 6–8 wks old	200 mg/kg Pb acetate through i.p. injection of Pb; one time injection	Testicular weight loss with constant increase in the incidence of abnormal sperm population; decrease in sperm count; testicular ascorbic acid also declined significantly; significant rise in LPP of tissue; LPP is indicative of oxidative stress in treated mice testes.	Not reported
Adhikari et al. (2000)	Rat/Druckrey, 28 days old	0.0, 0.4, 4.0, 40.0 µM Pb acetate in vitro for 24 and48 hr	Germ cells progressively detached from Sertoli cell monolayer into medium in a concentration and duration dependent manner Viability of the detached cells showed a decrease with increase in time and concentration of Pb; leakage of LDH recorded at higher dose of 4.0 and 40.0 µM.	PbB not applicable–in vitro study
Adhikari et al. (2001)	Rat/Druckrey, 28 days old	5, 10, and 20 mg/kg Pb in distilled water by gavage for2 wks	Induced significant numbers of germ cells to undergo apoptosis in the semiferous tubules of rats treated with highest dose; DNA fragmentation was not detected at any of the doses; level of Pb accumulation in testes increased in a dose-dependent manner.	PbB not reported
Alexaki et al. (1990)	Bulls/Holstein, 3–5 yrs old	In vitro fertilization 2.5 or 0.25 µg/mL	Sperm motility reduced significantly at 2.5 µg/mL; lower concentration had no effect on sperm motility.	PbB not applicable–in vitro study
Al-Hakkak et al. (1988)	Mouse/ BALB/c, weaning	0, 25, 50 mg Pb monoxide alloy/kg in chow for 35–70 days	Reduced number of spermatogenia and spermatocytes in the 50 mg group after 70 days; reduced number of implantations after mating (after 35 days exposure).	PbB not reported
Barratt et al. (1989)	Rat/Wistar, 70 days old	0, 0.3, 33, 330 mg Pb acetate/kg-d in drinking water, by gavage for 63 days	Increased number of abnormal post-testicular sperm in the highest exposure group; reduced number of spermatozoa at PbB >4.5 µg/dL.	PbB 2, 4.5, 7, 80 µg/dL PbBs >40 µg/dL
Bataineh et al. (1998)	Rat/Sprague Dawley, adult	1000 ppm Pb acetate in drinking water for 12 wks	Fertility was reduced in males.	PbB not reported
Batra et al. (2001)	Rat/Portan, 8 wks old	10, 50, 200 mg/kg Pb acetate orally for 3 mo	Pb in testis and epididymis increased with dose; administration of zinc reduced Pb levels; dose related changes in activities of enzyme alkaline phosphatase and Na+-K+- ATPase, which decreased with increased dose of Pb; improvement in activities of enzymes was seen in groups given Pb and zinc; disorganization and disruption of spermatogenesis with accumulation of immature cells in lumen of tubule; highest dose of Pb resulted in arrest of spermatogenesis, and decrease in germ cell layer population; highest dose levels, damage of basement membrane, disorganization of epithelium and vacuolization cells; tubules were found almost empty, indicating arrest of spermatogenesis.	PbB not reported
Batra et al. (2004)	Rat/Portan, 8 wks old	10, 50, 200 mg/kg Pb acetate orally for 3 mo	LH and FSH concentrations were decreased at 200 mg/kg; decrease in fertility status at 200 mg/kg; decline in various cell populations at 200 mg/kg; 50 mg/kg group hormone levels, cell numbers, and fertility status were found close to normal.	PbB not reported
Bizarro et al. (2003)	Mouse/CD-1, adult	0.01 M Pb acetate twice a week for 4 wks	Dose-time relationship was found; ROS role.	PbB not reported
Boscolo et al. (1988)	Rat/Sprague Dawley, weanling	60 mg Pb acetate/mL in drinking water for 18 mo	Increased vacuolization in Sertoli cells; no other ultrastructural modifications; no impairment of spermatogenesis.	PbB 4–17 µg/dL
Chowdhuri et al. (2001)	Mouse/ BALB/c, 3 mo old	0.0, 0.2, 0.5, 1.0, 2.0 µg/mL Pb acetate in culture medium for 2 hr (superovulated ova and sperm)	Significant dose dependent decrease in the number of sperm attaching to the ova in both exposed groups; decrease in the incorporation of radio-labeled thymdine, uridine, and methionine.	PbB not applicable–in vitro study
Chowdhury et al. (1984)	Rat/Albino, (NOS), adult	Dietary concentrations of 0.25, 0.50, or 1.0 g/L Pb acetate for 60 days	Testicular atrophy along with cellular degeneration was conspicuous at 1 g/L; high cholesterol concentration and significantly low ascorbic acid concentration were found in the testes at 1 g/L; lowest dose (0.25 g/L) had no significant morphological and spermatogenesis. biochemical alterations, whereas as 0.5 g/L resulted in partial inhibition of	PbB 54–143 µg/dL
Chowdhury et al. (1986)	Rat/NOS, adult	0, 1, 2, 4, 6 mg Pb acetate/kg-d i.p. for 30 days	Dose-related decrease of testis weight; at 187 µg/dL: degenerative changes in testicular tissues; at 325 µg/dL: degenerative changes and inquiry of spermatogenetic cells; edematous dissociation in interstitial tissue.	PbB 20, 62, 87, 187, or 325 µg/dL

Table AX5-4.2. Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Chowdhury et al. (1987)	Rat/Charles Foster, 150 ± 5 g	0, 1, 2, 4, 6 mg Pb acetate/kg-d/i.p. for 30 days	Dose related decrease of testis weight at 56 µg of spermatoids; at 91 µg/dL: inhibition of post-meiotic spermatogenic cell; at 196 µg/dL: decreased spermatogenic cell count (6), detachment of germinal call layers; at 332 µg/dL: Decreased spermatogenic cell count, degenerative changes, Interstitial edema, and atrophy of Leydig cells.	PbB 56–3332 µg/dL
Coffigny et al. (1994)†	Rat/Sprague-Dawley, adult	Inhalation exposure to 5 mg/m3 Pb oxide daily for 13 days during gestation(GD 2, 3, 6–10, 13–17, 20)	Adult male offspring exhibit no change in sperm parameters or sex hormones T, FSH, and LH (because of duration or timing).	PbB 71.1 µg/dL (dam) PbB 83.2 µg/dL (fetal)
Corpas et al. (1995)	Rat/Wistar, adult	300 mg/L Pb acetate via drinking water beginning GD1 through 5 days postnatal or throughout gestation and early lactation	Testicular weight and gross testicular structure were not altered; seminiferous tubule diameter and the number of prospermatogonia were reduced; total DNA, RNA, and protein content of the testes in treated rats was significantly reduced, DNA:RNA ratio remained unaltered.	PbB 14 µg/dL
Corpas et al. (2002a)	Rat/Wistar, adult	300 mg/L acetate Pb in drinking water beginning at mating until PND 12 and 21	Neither abnormalities in the liver structure nor depositions of Pb, toxicant produced biochemical alterations; pups exhibited decrease in hemoglobin, iron and alkaline, and acid phosphatase levels and an increase in Pb content; protein, DNA, and lipid total amounts were reduced, and hepatic glycogen content was diminished at 12 and 21 PN, with a higher dose of glucose in blood; decrease in alkaline phosphatase in liver of pups at day 21 PN, but acid phosphatase was unaltered.	PbB 22 µg/dL
Corpas et al. (2002b)	Rat/Wistar, adult	300 mg/L acetate Pb in drinking water beginning at mating until PND 12 and 21	Neither abnormalities in the liver structure nor depositions of Pb, toxicant produced biochemical alterations; pups exhibited decrease in hemoglobin, iron and alkaline, and acid phosphatase levels and an increase in Pb content; protein, DNA, and lipid total amounts were reduced, and hepatic glycogen content was diminished at 12 and 21 PN, with a higher dose of glucose in blood; decrease in alkaline phosphatase in liver of pups at day 21 PN, but acid phosphatase was unaltered.	PbB 22 µg/dL
Cory-Slechta et al. (2004)†	Rat/Long-Evans, adult	Pb acetate in drinking water beginning 2 mo before breeding until the end of lactation	Observed potential effects of Pb and stress in female; Pb alone (in male) and Pb plus stress (in females) permanently elevated corticosterene levels in offspring.	PbB 30–40 µg/dL
Foote (1999)	Rabbit/Dutch-belted, adult	0, 0.005, 0.01, and 0.025 mM PbCl2 in vitro; one time dose	Six out of 22 males tested showed appreciable spontaneous hyperactivation, Pb did not affect hyperactivation, or associated capacitation.	PbB not applicable–in vitro study
Foster et al. (1993)	Monkey/ Cynomolgus, adult	0–1500 µg Pb acetate/kg-d in gelatin capsules p.o. for various durations: 9 control monkeys, 4 monkeys in lifetime group (birth to 9 yrs), 4 in infancy group (first 400 days of life), 4 in post-infancy exposure (from 300 days to 9 yrs)	Suppressed LH response to GnRH stimulation in the lifetime group ($p = 0.0370$); Sertoli cell function (reduction in the inhibin to FSH ratio) ($p = 0.0286$) in lifetime and post-infancy groups.	Lifetime group 3–26 µg/dL at 4–5 yrs; infancy group 5–36 µg/dL at 100–300 days, 3–3 µg/dL at 4–5 yrs; post-infancy group 20–35 µg/dL
Foster et al. (1996a)	Monkey/ Cynomolgus, adult	0–1500 µg Pb acetate/kg-d in gelatin capsules p.o. from birth until 9 yrs of age: 8 control monkeys, 4 monkeys in low group (6-20 µg/dL), 7 monkeys in high group (22–148 µg/dL)	Mean PbB of 56 µg/dL showed no significant alterations in parameters of semen quality (count, viability, motility, or morphology).	PbB 10 ± 3 or 56 ± 49 µg/dL

Table AX5-4.2. Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Foster et al. (1998)	Monkey/ Cynomolgus, adult	0–1500 µg Pb acetate/kg-d in gelatin capsules p.o. for various durations: birth to 10 yrs (lifetime); PND 300 to 10 yrs (post-infancy); birth to 300 days (infancy); 3 control monkeys, 4 lifetime, 4 infancy, 5 post-infancy	Circulating concentrations of FSH, LH, and testosterone were not altered by treatment; semen characteristics (count, motility, morphology) were not affected by treatment possibly because not all Sertoli cells were injured; degeneration of seminiferous epithelium in infancy and lifetime groups (no difference in severity between these groups); ultrastructural alterations in seminal vesicles, most prominent in infancy and post-infancy groups.	PbB ~35 µg/dL
Gandley et al. (1999)	Rat/Sprague-Dawley, adult	Male rats received Pb acetate 25 or 250 ppm in drinking water for 35 days prior to mating	High dose reduced fertility; low dose altered genomic expression in offspring.	PbB 15–23 µg/dL or 27–60 µg/dL
Gorbel et al. (2002)	Rat/(NOS), 90 days old	3 mg (P1) or 6 mg (P2) Pb acetate in drinking water for 15, 30, 45, 60, or 90 days	Male rats, absolute and relative weights of testis, epididymis, prostate and seminal vesicles were found to significantly decrease at day 15 in P2 group and at day 45 in P1 group, at day 60 these absolute values and relative weights returned to control values; at day 15 arrest of cell germ maturation, changes in the Sertoli cells, and presence of apoptotic cells were observed; serum testosterone level was found to be lowered at day 15 in both P1 and P2, and peaked at day 60, then returned to normal values.	PbB not reported
Graca et al. (2004)	Mouse/CD-1, 2 mo old	Subcutaneous injection of 74 mg/kg-d of Pb chloride for1 to 3 days	Reversible changes in sperm (count) and ultrastructural changes in testes (reduced diameter of seminiferous tubules).	PbB not reported
Hsu et al. (1997)	Rat/Sprague Dawley, 7 wks old	10 mg/kg Pb acetate through i.p. injection to males for 6 or 9 wks	Six-week group had unchanged epididymal sperm counts, percent of motile sperms, and motile epididymal sperm counts compared with control group; 9-wk group showed statistically lower epididymal sperm counts, and lower motile epididymal sperm counts; good correlation between blood Pb and sperm Pb; significantly higher counts of chemiluminescence, they were positively associated with sperm Pb level; epididymal sperm counts, motility, and motile epididymal sperm counts were negatively associated with sperm chemiluminescence; SOPR were positively associated with epididymal sperm counts, motility and motile epididymal sperm counts, sperm chemiluminescence was negatively associated with SOPR.	PbB after 6 wks 32 µg/dL, after9 wks 48 ± 4.3 µg/dL
Hsu et al. (1998a)	Rat/Sprague Dawley, 100–120 g	20 or 50 mg Pb acetate via i.p. route weekly to males for 6 wks	Serum testosterone levels were reduced; percentage of capacitation and the chemiluminescence were significantly increased in fresh cauda epididymal spermatozoa; serum testosterone levels were negatively associated with the percentage of acrosome-reacted spermatozoa; sperm chemiluminescence was positively correlated with the percentage of both capacitated and acrosome-reacted spermatozoa; SOPR was negatively associated with the percentage of both capacitated and acrosome-reacted spermatozoa.	PbBs >40 µg/dL
Hsu et al. (1998b)	Rat/Sprague Dawley, 7 wks old	10 mg/kg Pb acetate weekly via i.p. injection to males for 6 wks	Intake of VE and/or VC in Pb exposed rats prevented the Pb associated sperm ROS generation, increased the epididymal sperm motility, enhanced the capacity of sperm to penetrate eggs harvested from unexposed female rats in vitro; protective effect of VE and VC not associated with reduced blood or sperm Pb levels.	PbB 30.1 ± 3.4 to 36.1 ± 4.6 PbBs >40 µg/dL
Huang et al. (2002)	Mouse MA-10 cells	10^{-8} to 10^{-5} M Pb incubated for 3 hr	Higher decreases in human chorionic gonadotropin (hCG)-stimulated progesterone production, expressions of StAR protein, and the activity of 3ß-HSD compared to 2 hr; no affect on P450scc enzyme activity.	PbB not applicable–in vitro study
Johansson (1989)	Mouse, 9 wks old	0–1 g Pb chloride/L in drinking water for 112 days	No effects on frequency of motile spermatozoa, nor on swimming speed; decreased fertilizing capacity of the spermatozoa by in vitro fertilization; premature acrosome reaction .	PbB 0.5–40 µg/dL
Johansson and Pellicciari	Mouse/NMRI, 9 wks old	1 g/L Pb chloride in drinking water for 16 wks	Decreased uptake of PI was found in spermatozoa from the vas deferens of the Pb- exposed mice; after thermal denaturation of the DNA, the spermatozoa showed a higher uptake of PI in	PbB 42 ± 1.6 µg/dL

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Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
(1988)			comparison to those of the controls; after reductive cleavage of S-S bonds with DTT and staining with a thiol-specific reagent significantly fewer reactive disulfide bonds were also observed in the spermatozoa; significant delay in the capacity for NCD was noted.	
Johansson and Wide (1986)	Mouse/NMRI, 9 wks old	0–1 g/L Pb chloride in drinking water for 84 days	No effects on sperm count; no effects on serum testosterone; reduced number of implantations after mating.	PbB <0.5–32 µg/dL Mean tissue Pb content difference between Pb treated and controls: testicular 11 µg/g (epididymal 67 µg/g) PbB <0.5 µg/100 mL
Johansson et al. (1987)	Mouse/NMRI, 9–10 wks old	1 g/L Pb chloride in drinking water for 16 wks	Spermatozoa had significantly lower ability to fertilize mouse eggs; morphologically abnormal embryos were found.	PbB not reported
Kempinas et al. (1988)	Rat/Wistar, adult	0.5 g/L and 1.0 g/L Pb acetate in drinking water for 90 days	PbB exhibited a significant increase in both groups; decrease in hematocrit and hemoglobin, together with a rise in glucose levels; no signs of lesion were detected upon histological examination of testes, caput, and cauda epididymidis; an increase in ductal diameter, and a decrease in epithelial height were observed in the cauda epididymidis; concentration of spermatozoa stored in the caudal region of the epididymis exhibited a significant increase in Pb-treated animals.	PbB 65–103 µg/dL
Kempinas et al. (1990)	Rat/NOS, pubertal	(1.0 g/L) Pb acetate in drinking water in addition to i.v. injections of Pb acetate(0.1 mg/100 g bw) every 10 days, 20 days (1.0 g/L) Pb acetate in drinking water in addition to i.v. injections of Pb acetate (0.1 mg/100 g bw) every15 days, 9 mo	Basal levels of testosterone were higher both in the plasma and in the testes of acutely intoxicated animals; levels of LH were not affected in either group, nor was the LHRH content of the median eminence; density of LH/hCG binding sites in testicular homogenates was reduced by saturnism in both groups, apparent affinity constant of the hormone-receptor, complex significantly increased.	PbB ~40 µg/dL
Kempinas et al. (1994)	Rat/Wistar, 50 days old	0–1 g Pb acetate/L in drinking water + 0.1 mg/kg i.v. every 10 days for 20 days 0–1 g Pb acetate/L in drinking water + 0.1 µg/kg i.v. every 15 days for270 days	Increased plasma and testicular testosterone concentrations; no effects on testicular weight; reduced weight of prostate; increased weight of seminal vesicle and seminal secretions.	PbB 10–41 µg/dL PbB 8.5–40 µg/dL
Klein et al. (1994)	Rat/Sprague-Dawley, 100 days old	0.1, 0.3, or 0.6% Pb acetate in distilled water for 21 days	2–3-fold enhancement of mRNA levels of GnRH and the tropic hormone LH; 3-fold enhancement of intracellular stores of LH; mRNA levels of LH and GnRH and pituitary levels of stored LH are proportional to blood levels of Pb.	PbB 42–102 µg/dL
Liu et al. (2001)	Mouse, MA-10 cells	10^{-8} to 10^{-5} Pb acetate in vitro for 2 hr	Significantly inhibited hCG- and dbcAMP-stimulated progesterone production in MA-10 cells; steroid production stimulated by hCG or dbcAMP were reduced by Pb; expression of StAR protein and the activities of P450 side-chain cleavage (P450) and 3ß-HSD enzymes detected; expression of StAR protein stimulated by bdcAMP was suppressed by Pb at about 50%; progesterone productions treated with 22R hydroxycholesterol or pregnenolone were reduced 30–40% in Pb treated MA-10 cells.	PbB not applicable–in vitro study
Liu et al. (2003)	Mouse, MA-10 cells	10^{-8} to 10^{-5} Pb acetate in vitro for 6 hr incubated	Pb significantly inhibited hCG- and dbcAMP-stimulated progesterone production from 20 to 35% in MA-10 cells at 6 hr; Pb suppressed the expression of steriodogenesis acute regulatory (StAR) protein from 30 to 55%; activities P450 side-chain cleavage (P450scc) enzyme and 3ß-HSD were reduced by Pb from 15 to 25%.	PbB not applicable–in vitro study
Marchlewicz et al. (1993)	Rat/Wistar, 90 days old	0–1% Pb acetate in drinking water for 270 days	No histological or weight changes in testicle or epididymis; fever spermatozoa in all zones of the epididymis.	PbB not reported
McGivern et al. (1991)†	Rat/Sprague-Dawley, adult	0.1% Pb acetate in drinking water from GD 14 to parturition: 8 control litters; 6	Decreased sperm count (21% at 70 days and 24% at 165 days; $p < 0.05$); reduced male behavior ($p < 0.05$); enlarged prostate (25% increase in weight; $p < 0.07$); irregular release patterns of both FSH and LH ($p < 0.05$).	Control PbB <5 µg/dL at birth Maternal PbB 73 µg/dL at birth

Table AX5-4.2. Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
		Pb acetate litters (5 males per litter)		Pup PbB 64 µg/dL at birth
McMurry et al. (1995)	Rat/Cotton, adult	0, 100, or 1000 ppm Pb in drinking water for 7 or13 wks	Immune function was sensitive to Pb exposure; spleen mass was reduced in cotton rats receiving 100 ppm Pb; total leukocytes, lymphocytes, neutrophils, eosinophils, total splenocyte yield, packed cell volume, hemoglobin, and mean corpuscular hemoglobin were sensitive to Pb exposure; reduced mass of liver, seminal vesicles, and epididymis in males after 7 wk exposure.	PbB not reported
Mishra and Acharya(2004)	Mouse/Swiss, 9–10 wks old	10 mg/kg Pb acetate in drinking water for 5 to 8 wks	Stimulates lipid peroxidation in the testicular tissue, associated with increased generation of noxious ROS; reduced sperm count, increased sperm abnormality	PbB not reported
Moorman et al. (1998)	Rabbit/NOS, adult	3.85 mg/kg Pb acetate subcutaneous injection for 15 wks	Increased blood levels associated with adverse changes in the sperm count, ejaculate volume, percent motile sperm, swimming velocities, and morphology; hormonal responses were minimal; dose-dependent inhibition of sperm formation; semen quality, threshold estimates ranged from 16 to 24 µg/dL.	PbB 0, 20, 40, 50, 70, 80, 90, and 110 µg/dL
Murthy et al. (1991)	Rat/ITRC, (NOS), weanling	0–250 ppm Pb acetate in drinking water for 70 days	At 20 µg/dL no impairment of spermatogenesis; vacuolization of Sertoli cell cytoplasm and increase in number and size of lysosomes.	PbB 20.34 ± 1.79 µg/dL
Murthy et al. (1995)	Rat/Druckrey, adult	Pb 5 mg/kg i.p. Pb acetate in drinking water for 16 days	Swelling of nuclei and acrosomes round spermatids; in Sertoli cells, nuclei appeared fragmented, whereas the cytoplasm exhibited a vacuolated appearance and a few structures delimitated by a double membrane that contains microtubules arranged in parallel and cross-striated fin fibrils, cell tight junction remain intact; no significant change in epididymal sperm motility and counts, testicular blood levels were found to be elevated after Pb exposure.	PbB 7.39 µg/dL
Nathan et al. (1992)	Rat/Sprague Dawley, adult	0, 0.05, 0.1, 0.5, or 1% Pb acetate in drinking water for70 days	No effects on spermatogenesis in all groups; at 124 µg/dL: decreased seminal vesicle weight; decreased serum testosterone in the 0.5% group at 10 wks; no effects in the other exposure categories; no effects on serum FSH, LH, nor pituitary LH content.	PbB 2.3, 40, 44, 80, or 124 µg/dL
Pace et al. (2005)	Mouse/BALB/c, adult	0.1 ppm Pb acetate in drinking water (lactational exposure as neonates and drinking water from PND 21 to PND 42)	Reduction in fertility when mated with unexposed females; no change in sperm count; increase in number of apoptotic cells in testes.	Neonatal PbB 59.5 µg/dL Post PND 21 PbB 20.3 µg/dL
Piasecka et al. (1995)	Rat/Wistar, adult	1% aqueous solution of Pb acetate for 9 mo	Pb-loaded (electron dense) inclusions were found in the cytoplasm of the epididymal principal cells, especially in the caput of epididymis, also present, but smaller, in smooth muscle cells; inclusions were located in the vacuoles, rarely without any surrounding membrane; similar Pb-containing structures were found in the epididymal lumen.	PbB not reported
Piasek and Kostial (1987)	Rat/Albino, (NOS), adult	1500, 3500, and 5500 ppm of Pb acetate in drinking water for 18 wks	No overt signs of general toxicity in adult female rats, only at the end of the exposure period the mean body weight of males exposed to two higher levels was slightly lower; no effect of Pb exposure on male fertility either after first or after second mating; values in the pups did not differ from control group.	PbB not reported
Pinon-Lataillade et al. (1993)	Rat/Sprague Dawley, 90 days old	0–0.3% Pb acetate in drinking water for 70 days 5 mg/m2 Pb oxide in aerosol for 6 hr/day, 5 days/wk, 90 days	Decreased weight of seminal vesicles in inhalation study; no effects on spermatogenesis (epididymal sperm count, spermatozoal motility or morphology) or plasma testosterone, LH, and FSH; no effects on fertility; decrease in epididymal sperm count of progeny of sires of the inhalation group, however without effect on their fertility.	PbB 58 ± 1.7 µg/dL (oral) PbB 51.1 ± 1.8 µg/dL (inhalation)
Pinon-Lataillade et al. (1995)	Mouse/NMRI, adult	0–0.5% Pb acetate in drinking water, day 1 of gestation until 60 days of age	No effects on testicular histology, nor on number and morphology of epididymal spermatozoa; no effects on plasma FSH, LH, and testosterone, nor on testicular testosterone; decreased weight of testes, epididymis, seminal vesicles, and ventral prostate; no effects on fertility.	PbB <4–132 µg/dL
Rodamilans et al. (1988)	Mouse/BALB/c, 63 days old	0–366 mg Pb acetate/L in drinking water for 30, 60, 90, 120, 150, 180 days	Reduction of intratesticular testosterone concentrations after 30 days; reduction of and renostenedione concentrations after 150 days; no changes in intratesticular progesterone and hydroxy-progesterone.	PbB 48–67 µg/dL

Table AX5-4.2. Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Ronis et al. (1996)†	Rat/Sprague-Dawley, adult	0.6% Pb acetate in drinking water for various durations: PND 24–74 (pubertal exposure); PND 60–74 (post pubertal exposure); 11 males and females in pubertal exposure group (10 each in control pubertal group); 6 males and females post pubertal exposure and control groups	PbB > 250 µg/dL reduced circulating testosterone levels in male rats 40–50% ($p < 0.05$); reduction in male secondary sex organ weight ($p < 0.005$); delayed vaginal opening ($p < 0.0001$); disrupted estrous cycle in females (50% of rats); increased incidence of stillbirth (2% control vs. 19% Pb) ($p < 0.005$).	Pubertal PbB 30–60 µg/dL Post pubertal PbB 30–60 µg/dL Mean PbBs in male rats 30– 60 µg/dL, respectively
Ronis et al. (1998a)	Rat/Sprague Dawley, adult	0.6% Pb acetate in drinking water ad libitum for various durations as follows: GD 5 to PND 1; GD 5 to weaning; PND 1 to weaning; 3 control litters, 2 gestation exposure litters, 2 lactation exposure litters, 2 gestation and lactation exposure litters, 2 postnatal exposure litters, 2 chronic exposure litters; 4 male and 4 female pups per litter.	Suppression of adult mean serum testosterone levels was only observed in male pups exposed to Pb continuously from GD 5 throughout life ($p < 0.05$).	Group: male PbB Naïve: 5.5 ± 2.0 µg/dL Control: 1.9 ± 0.2 µg/dL Gest: 9.1 ± 0.7 µg/dL Lact: 3.3 ± 0.4 µg/dL Gest+Lact: 16.1 ± 2.3 µg/dL Postnatal: 226.0 ± 29 µg/dL Chronic: 316.0 ± 53 µg/dL
Ronis et al. (1998b)	Rat/Sprague-Dawley, adult	Pb acetate in drinking water (0.05% to 0.45% w/v); dams exposed until weaning, exposure of pups which continued until PND 21, 35, 55, or 85; 5 control litters (0%), 10 low-dose litters (0.05%), 8 mid-dose litters (0.15%), 9 high-dose litters (0.45%); 4 male and 4 female pups per litter	Dose-response reduction in birth weight ($p < 0.05$), more pronounced in male pups; decreased growth rates in both sexes ($p < 0.05$) were accompanied by a statistically significant decrease in plasma concentrations of IGF1 through puberty PND 35 and 55 ($p < 0.05$); increase in pituitary growth hormone during puberty ($p < 0.05$).	Mean PbB in offspring at 0.05% (w/v) 49 ± 6 µg/dL Mean PbB in offspring at 0.15% (w/v) 126 ± 16 µg/dL Mean PbB in offspring at 0.45% (w/v) 263 ± 28 µg/dL
Ronis et al. (1998c)†	Rat/Sprague-Dawley, adult	Pb acetate 0.05, 0.15, or 0.45% in drinking water beginning GD 5 continuing until PND 21, 35, 55, or 85; 5 control litters (0%), 10 low-dose litters (0.05%), 8 mid-dose litters (0.15%), 9 high-dose litters (0.45%); 4 male and 4 female pups per litter	Dose-responsive decrease in birth weight ($p < 0.05$); dose-responsive decrease in crown-to-rump length ($p < 0.05$); dose-dependent delay in sexual maturity ($p < 0.05$); decrease in prostate weight ($p < 0.05$); decrease in plasma concentration of testosterone during puberty ($p < 0.05$); decrease in plasma LH ($p < 0.05$); elevated pituitary LH content ($p < 0.05$); decrease in plasma testosterone/LH ratio at high dose ($p < 0.05$).	Dams: 0, 48, 88, or 181 µg/dL Pups PND 1: <1, 40, 83, or 120 µg/dL Pups PND 21: <1, 46, 196, or 236 µg/dL Pups PND 35: <1, 20, 70, or 278 µg/dL Pups PND 55: <1, 68, 137, or 379 µg/dL Pups PND 85: <1, 59, 129, or 214 µg/dL
Sant'Ana et al. (2001)	Rat/Wistar, 90 days old	0.1 and 1% Pb acetate in drinking water for 7 days	0.1% Pb caused decrease in testis weight, an increase in seminal vesicle weight and no changes in plasma testosterone levels, hypothalamic VMA levels were increased compared to control group.	PbB 36.12 ± 9.49 µg/dL and 13.08 ± 9.42 µg/dL

Table AX5-4.2. Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Saxena et al. (1984)	Rat/ITRC, albino (NOS), 12 wks old	8 mg/kg Pb acetate i.p. for 15 days	Histoenzymic and histological alterations in the testes; degeneration of seminiferous tubules; patchy areas showing marked loss in the activity of succinic dehydrogenase and adenosine triphosphatase, whereas alkaline phosphatase activity showed only slight inhibition.	PbB not reported
Saxena et al. (1986)	Rat/ITRC, albino (NOS), 40–50 g	5, 8, or 12 mg Pb+2/kg Pb acetate i.p. for 15 days	Increasing dose of Pb resulted in significant loss of body weight, as well as testicular weight in groups 3 and 4; cholesterol in the testis of rats markedly decreased at all given doses of Pb and was statistically significant in groups 3 and 4; in phospholipid contents, the significant decrease was observed only at two highest doses, while at the lowest dose the decrease was not significant; activity of ATPase remained unaffected at all three doses of Pb; no significant increase in Pb content in the testis was noticed at lower dose levels as compared to control; however, significant increase was found in groups 3 and 4 which was dose dependent.	PbB not reported
Saxena et al. (1987)	Rat/Wistar, 40–50 g	8 mg Pb2/kg-d Pb acetate i.p. for 100 days (from PND 21 to PND 120)	Disturbed spermatogenesis; Leydig cell degeneration; altered enzyme activity (G6PDH).	PbB not reported
Saxena et al. (1990)	ITRC albino, (NOS), adult	8 mg/kg/d Pb acetate for 45 days	Alterations in SDH, G6PDH activity, cholesterol, and ascorbic acid contents and reduced sperm counts associated with marked pathological changes in the testis, after combined treatment with Pb and immobilization stress in comparison to either alone.	PbB >200 µg/dL
Singh et al. (1993a)	Monkey/ Cynomolgus, birth Birth: 300 days:	0–1500 µg Pb acetate/kg-d in gelatin capsules for various durations: 3 control monkeys, 4 monkeys in infancy group (exposure first 400 days), 5 in post-infancy group (exposure 300 days to 9 yrs of age), 4 in lifetime group (exposure from birth until 9 yrs)	Degeneration of seminiferous epithelium in all exposed groups (frequency not specified); ultrastructural alterations in seminal vesicles, most prominent in infancy and post-infancy groups (frequency not specified).	Chronic PbB <40–50 µg/dL
Sokol (1987)	Rat/Wistar, 52 days old	0–0.3% Pb acetate in drinking water for 30 days	Hyper-responsiveness to stimulation with both GnRH and LH (10); blunted response to naloxone stimulation (10).	PbB 30 ± 5 µg/dL
Sokol (1989)	Rat/Wistar, 27 days old	0–0.6% Pb acetate in drinking water for 30 days + 30 days recovery	Suppressed intratesticular sperm counts, sperm production rate, and serum testosterone in both Pb treated groups (10–10); sperm parameters and serum testosterone normalized at the end of the recovery period in the pre-pubertal animals (27 days at start) (10) but not in the pubertal animals (52 days at start) (5).	<3–43 µg/dL (<4–18 µg/dL after recovery period)
	52 days old	0–0.6% Pb acetate in drinking water for 30 days + 30 days recovery		B1 <3–43 µg/dL (<4–18 µg/dL after recovery period)
Sokol (1990)	Rat/Wistar, 52 days old	0–0.6% Pb acetate in drinking water for 7, 14, 30, 60 days	Decreased sperm concentration, sperm production rate and suppressed serum testosterone concentrations after 14 days of exposure; not dose related (NS).	Controls: <8 µg/dL at any time exposed: 42, 60, 58, 75 µg/dL after 7, 14, 30, and 60 days, respectively
Sokol and Berman (1991)	Rat/Wistar, NOS	0, 0.1, or 0.3% Pb acetate in drinking water for 30 days beginning at 42, 52, or 70 days old; 8–11 control rats for each age, 8–11 rats for each age in 0.1% group, 8– 11 rats for each age in 0.3% group	Dose-related suppression of spermatogenesis (decreased sperm count and sperm production rate) in the exposed rats of the two highest age groups ($p < 0.05$); dose-related suppression of serum testosterone in 52-day old rats ($p = 0.04$) and in 70-day old rats ($p < 0.003$).	0% All <7 µg/dL 42 days 25 µg/dL 0.1% 52 days 35 µg/dL 70 days 37 µg/dL 42 days 36 µg/dL

Table AX5-4.2. Effect of Lead on Reproduction and Development in Mammals Effects on Males

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
				0.3% 52 days 60 µg/dL 70 days 42 µg/dL
Sokol et al. (1985)†	Rat/Wistar, 52 days old	0.1 or 0.3% Pb acetate in drinking water for 30 days	Negative correlations between PbB levels and serum and intratesticular testosterone values; dose-dependent reduction in intratesticular sperm count; FSH values were suppressed; no change in LH; decrease in ventral prostatic weight; no difference in testicular or seminal vesicle weights.	PbB 34 ± 3 µg/dL or PbB 60 ± 4 µg/dL
Sokol et al. (1994)	Rat/Sprague Dawley, 100 days old	0.3% Pb acetate in drinking water for 14, 30, or 60 days	Pb exposed fertilized fewer eggs; increased duration of exposure did not result in more significant percentage of eggs not fertilized; no ultrastructural changes were noted in the spermatozoa of animals; no difference in histogram patterns of testicular cells.	PbB ~40 µg/dL
Sokol et al. (2002)	Rat/Sprague-Dawley, adult	Pb acetate in water for 1 wk	Dose-related increase in gonadotropin-releasing hormone (GnRH) mRNA; no effect on the serum concentrations of hypothalamic gonadotropin-releasing hormone (GnRH) or LH.	PbB 12–28 µg/dL
Thoreux-Manlay et al. (1995a)	Rat/Sprague Dawley, 97 days old	0–8 mg Pb acetate/kg i.p. for 5 days/wk, 35 days	No effects on spermatogenesis; decreased plasma and testicular testosterone by 80%; decreased plasma LH by 32%, indications for impaired Leydig cell function, no effects on fertility.	PbB not reported
Thoreux-Manlay et al. (1995b)	Rat/Sprague Dawley, adult	8 mg/kg-d Pb for 5 days/wk, 35 days	Germ cells and Sertoli cells were not major target of Pb, accessory sex glands were target; epididymal function was unchanged; plasma and testicular testosterone dropped about 80%, plasma LH only dropped 32%.	PbB 1700 µg/dL
Wadi and Ahmad (1999)	Mouse/CF-1, adult	0.25 and 0.5% Pb acetate in drinking water for 6 wks	Low dose significantly reduced number of sperm within epididymis; high dose reduced both the sperm count and percentage of motile sperm and increased the percentage of abnormal sperm within the epididymis; no significant effect on testis weight, high dose significantly decreased the epididymis and seminal vesicles weights as well as overall body weight gain; LH, FSH, and testosterone were not affected.	PbB not reported
Wenda-Rózewicka et al. (1996)	Rat/Wistar, adult	1% aqueous solution of Pb acetate for 9 mo	Electron microscopic studies did not reveal any ultrastructural changes in the semiferous epithelium or in Sertoli cells; macrophages of testicular interstitial tissue contained (electron dense) Pb-loaded inclusions, usually located inside phagolisosome like vacuoles; x-ray micro-analysis revealed that the inclusions contained Pb.	PbB not reported
Yu et al. (1996)	Rat/Sprague-Dawley, neonates	Neonatal and lactational exposure to 0.3% Pb acetate in drinking water beginning PND 1 to PND 21	Neonatal exposure to Pb decreased cold-water swimming endurance (a standard test for stress endurance) and delayed onset of puberty in males and female offspring, which was exacerbated by swimming stress.	PbB 70 µg/dL

*Not including effects on the nervous or immune systems.

† Candidate key study.

3ß-HSD, 3ß-hydroxysteriod dehydrogenase; dbcAMP, dibutyryl cyclic adenosine-3',5'-monophosphate; DTT, dithiothreitol; FSH, follicle stimulating hormone; G6PDH, glucose-6-phosphate dehydrogenase; GD, gestational day; GnRH, gonadotropin releasing hormone; hCG, human chorionic gonadotropin; IGF_1, insulin-like growth factor 1; i.p., intraperitoneal; LDH, lactate dehydrogenase; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; LPP, lipid peroxidation potential; NCD, nuclear chromatin decondensation rate; NOS, not otherwise specified; PbB, blood lead concentration; PND, post-natal day; p.o., per os (oral administration); ROS, reactive oxygen species; SDH, succinic acid dehydrogenase; SOPR, sperm-oocyte penetration rate; StAR, steroidogenic acute regulatory protein; VC, vitamin C; VE, vitamin E; VMA, vanilmandelic acid

Table AX5-4.3. Effect of Lead on Reproduction and Development in Mammals Effects on Females

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Burright et al. (1989)	Mouse/HET, neonates	0.5% Pb acetate solution via milk, or drinking water chronic beginning PND 1	Plasma prolactin levels implied that Pb exposure alone decreased circulating prolactin in primiparous; low prolactin levels in non-behaviorally tested females suggests that dietary Pb alone may alter plasma-hormone in these lactating HET dams; pattern of plasma prolactin appear to be inconsistent with the observation that Pb exposure decreases dopamine; prolactin levels of Pb exposed dams were very low.	PbB ~100 µg/dL
Coffigny et al. (1994)†	Rat/Sprague-Dawley, adult	Inhalation exposure to 5 mg/m3 Pb oxide daily for 13 days during gestation (GD 2, 3, 6–10, 13–17, 20)	No effects on the incidence of pregnancy, prenatal death, or malformations when male and female rats from mothers who had been exposed.	PbB 71.1 µg/dL (dam) PbB 83.2 µg/dL (fetal)
Corpas et al. (2002a)	Rat/Wistar, adult	300 mg/L acetate Pb in drinking water from mating until PND 12 or PND 21	Neither abnormalities in the liver structure nor depositions of Pb, toxicant produced biochemical alterations; pups exhibited decrease in hemoglobin, iron and alkaline, and acid phosphatase levels and an increase in Pb content; protein, DNA, and lipid total amounts were reduced, and hepatic glycogen content was diminished at 12 and 21 PN, with a higher dose of glucose in blood; decrease in alkaline phosphatase in liver of pups at day 21 PN, but acid phosphatase was unaltered.	PbB 22 µg/dL
Cory-Slechta et al. (2004)†	Rat/Long-Evans, adult	Pb acetate in drinking water beginning 2 mo before breeding through weaning	Observed potential effects of Pb and stress in female; Pb alone (in male) and Pb plus stress (in females) permanently elevated corticosterene levels in offspring.	PbB 30–40 µg/dL
Dearth et al. (2002)†	Rat/Fisher 344, 150–175 g	12 mg/mL Pb acetate gavage from 30 days prior breeding until pups were weaned 21 days after birth; 10– 32 litters per group, control group, gestation and lactation exposure, gestation only exposure, lactation only exposure	Delay in onset of puberty ($p < 0.05$); reduced serum levels of IGF1 ($p < 0.001$), LH ($p < 0.001$), and E2 ($p < 0.001$).	Maternal PbB: ~40 µg/dL Pups PbB as follows: Gest+lact: ~38 µg/dL PND 10 Gest+lact: ~15 µg/dL PND 21 Gest+lact: ~3 µg/dL PND 30 Gest: ~14 µg/dL PND 10 Gest: ~3 µg/dL PND 21 Gest: ~1 µg/dL PND 30 Lact: ~28 µg/dL PND 10 Lact: ~15 µg/dL PND 21 Lact: ~3 µg/dL PND 30
Dearth et al. (2004)	Rat/Sprague-Dawley and Fisher-344, adult	12 mg/mL Pb acetate by gavage 30 days prior to breeding through PND 21 (gestation and lactation exposure)	Pb delayed the timing of puberty in PbB 37.3 µg/dL Pb group and suppressed serum levels of LH and E2, these effects did not occur in PbB 29.9 µg/dL Pb group, when doubling dose to 29.9 µg/dL group the PbB levels rose to 62.6 µg/dL, yet no effect was noted; results indicate that offspring are more sensitive to maternal Pb exposure with regard to puberty related insults than are 29.9 µg/dL rats.	PbB 29.9 µg/dL (Sprague-Dawley) PbB 37.3 µg/dL (Fisher)
Foster (1992)	Monkey/ Cynomolgus, 0–10 yrs old	Daily dosing for up to 10 yrs with gelatin capsules containing Pb acetate (1.5 mg/kg); 8 control group monkeys, 8 lifetime exposure (birth–10 yrs), 8 childhood exposure (birth–400 days), and 8 adolescent exposure (postnatal day 300–10 yrs of age)	Statistically significant reductions in circulating levels of LH ($p < 0.042$), FSH ($p < 0.041$), and E2 ($p < 0.0001$) during menstrual cycle; progesterone concentrations were unchanged and menstrual cycle was not significantly affected.	PbB <40 µg/dL

Table AX5-4.3. Effect of Lead on Reproduction and Development in Mammals Effects on Females

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Foster et al. (1992)	Monkey/ Cynomolgus, 10 yrs old	Daily dosing for up to 10 yrs with gelatin capsules containing Pb acetate (1.5 mg/kg); 8 control group monkeys, 8 childhood (birth– 400 days), 7 adolescent (postnatal day 300–10 yrs), 7 lifetime (birth–10 yrs)	No effect on endometrial response to gonadal steroids as determined by ultrasound.	PbB <40 µg/dL
Foster et al. (1996b)	Monkey/ Cynomolgus, 15–20 yrs old	Chronic exposure to Pb acetate 50 to 2000 µg/kg-d p.o. beginning at birth for 15–20 yrs; 20 control monkeys, 4 monkeys in 50 µg/kg-d group, 3 monkeys in 100 µg/kg-d, 2 monkeys in 500 µg/kg-d group, and 3 monkeys in 2000 µg/kg-d group	Reduced corpora luteal production of progesterone ($p = 0.04$), without alterations in E2, 20alpha-hydroxyprogesterone, or menstrual cyclicity.	PbB 10–15 µg/dL in low group (50 or 100 µg/kg-d) PbB 25–30 µg/dL in moderate group (500 or 2000 µg/kg-d)
Franks et al. (1989)	Monkey/Rhesus, adult	Pb acetate in drinking water (2–8 mg/kg-d) for 33 mo; 7 control and 10 Pb monkeys	Reduced circulating concentration of progesterone ($p < 0.05$); treatment with Pb did not prevent ovulation, but produced longer and more variable menstrual cycles and shorter menstrual flow.	PbB 68.9 ± 6.54 µg/dL
Fuentes et al. (1996)	Mouse/Swiss, adult	14, 28, 56, and 112 mg/kg Pb acetate via i.p; one time exposure on GD 9	Absolute placental weight at 112 mg/kg and relative placental weight at 14, 56, and 112 mg/kg were diminished significantly; most sections of placenta showed vascular congestion, and increase of intracellular spaces, and deposits of hyaline material of perivascular predominance; trophoblast hyperplasia was also observed, whereas there was a reinforcement of the fibrovascular network in the labyrinth	PbB not reported
Gorbel et al. (2002)	Rat/NOS, 3 mo old	3 mg (P1) or 6 mg (P2) Pb acetate in drinking water for 15, 30, 45, 60, or 90 days	Female rats absolute and relative weights of ovary and uterus were unchanged, vaginal smears practiced in females revealed the estrus phase; fertility was found to be reduced; Pb level in blood was poorly correlated with the level of poisoning.	PbB not reported
Iavicoli et al. (2004)	Mouse/Swiss, 33–37 days old	0.02, 0.06, 0.11, 0.20, 2.00, 4.00, 20.00, 40.00 ppm in food Pb acetate concentration beginning GD 1 to 3 mo after birth	Increase in food consumption; however, did low-dose group increase food consumption because of sweet nature of Pb. Body weight may contribute to delay in onset of puberty and confound results.	PbB 0.69, 1.32, 1.58, 1.94, 3.46, 3.80, 8.35, 13.20 µg/dL
Junaid et al. (1997)	Mouse/Swiss, adult	0, 2, 4, or 8 mg/kg-d Pb acetate, subchronic exposure, 5 days/wk, 60 days	Altered follicular development.	PbB 22.3–56.5 µg/dL
Laughlin et al. (1987)	Monkey/Rhesus, adult	Pb acetate in drinking water at 3.6, 5.9, or 8.1 mg/kg-d for1–2 yrs; 7 control and 10 experimental monkeys per group	Reductions in cycle frequency ($p < 0.01$); fewer days of flow ($p < 0.01$); longer and more variable cycle intervals ($p < 0.025$).	PbB 44–89 µg/dL 51.2 µg/dL (low dose) 80.7 µg/dL (mid dose) 88.4 µg/dL (high dose)
Lögdberg et al. (1987)	Monkey/ Squirrel, adult	Pb acetate in drinking water from 9th week of gestation to PND 1; per oral exposure similar to Laughlin et al. (1987)	Increase in pre-and perinatal mortality during the last two-thirds of pregnancy; statistically significant reduction in mean birth weight was observed in Pb exposed monkeys as compared to controls.	Mean maternal PbB 54 µg/dL (39–82 µg/dL)
Lögdberg et al. (1988)	Monkey/ Squirrel, adult	Pb acetate maternal dosing from 5–8.5 wks pregnant to PND 1 11 control monkeys, 3 low Pb exposure group (PbB24 µg/dL), 7 medium Pb group (PbB 40 µg/dL, 5 high- Pb group (PbB 56 µg/dL)	Dose-dependent reduction in placental weight ($p < 0.0007$); various pathological lesions were seen in the placentas, including hemorrhages, hyalinization of the parenchyma with destruction of the villi, and massive vacuolization of chorion epithelium.	PbB 37 µg/dL (22–82 µg/dL) 24 (22–26) µg/dL (low dose) 40 (35–46) µg/dL (mid dose) 56 (43–82) µg/dL (high dose)
McGivern et al. (1991)†	Rat/Sprague-Dawley, adult	0.1% Pb acetate in drinking water from GD 14 to parturition	Female rats showed delay in vaginal opening; 50% exhibited prolonged and irregular periods of diestrous and lack observable corpora lutea; both sexes showed irregular release patterns of both FSH and LH.	PbB 73 µg/dL

Table AX5-4.3. Effect of Lead on Reproduction and Development in Mammals Effects on Females

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
Nilsson et al. (1991)	Mouse/NMRI, adult	75 µg/g bw Pb chloride via i.v.; one time injection on GD 4	Electron microscopy showed that the uterine lumen, which was closed in control mice, was opened in Pb-injected mice; suggested that Pb caused increase in uterine secretion; study suggested Pb could have a direct effect on the function of the uterine epithelium and that Pb was secreted into the uterine lumen and affect the blastocysts.	PbB not reported
Piasek and Kostial(1991)	Rat/Wistar, 10 wks old	7500 ppm Pb acetate in drinking water for 9 wks	Decrease in litter size, pup survival, and birth weight; food consumption, body weight, and fertility were not altered in 20 wk exposure period.	Maternal PbB >300 µg/dL Offspring PbB >220 µg/dL
Pinon- Lataillade et al. (1995)	Mouse/NMRI, adult	0–0.5% Pb acetate in drinking water exposed to Pb during gestation until post- GD 60	Exhibited reduced fertility as evidenced by smaller litters and fewer implantation sites.	PbB 70 µg/dL
Priya et al. (2004)	Rat/Charles Foster, 6–9 mo old	0.03 µM Pb in vitro for 1 h	LH binding was dropped to 84% in Pb treated cells; Pb exposed cells showed 31% reduction in the enzymes 17ß-HSDH and 17ß-HS; Pb can cause a reduction in LH and FSH binding, which significantly alters steroid production in vitro and exerts a direct influence on granulose cell function.	PbB not applicable–in vitro study
Ronis et al. (1996)	Rat/Sprague-Dawley, various ages	Pb acetate in the drinking water or male and female rats for the following durations: PND 24–74 (pubertal exposure); PND 60–74 (post pubertal exposure)	Data suggest that both the temporary and the long-lasting effects of Pb on reproductive endpoints in male and female experimental animals are mediated by the effects of Pb on multiple points along the hypothalamic-pituitary-gonad axis; exposure of male and female Sprague-Dawley rats pre-pubertally (age 24–74 days) to Pb acetate in the drinking water resulted in significant reduction in testis weight and in the weight of secondary sex organs in males; these effects were not observed in rats exposed post pubertally (day 60–74); there is convincing evidence that pre-pubertal female rats exposed in utero and during lactation have reduced levels of circulating E2 and LH.	Maternal PbB 30–60 µg/dL Offspring PbB >200 µg/dL
Ronis et al. (1998a)†	Rat/Sprague-Dawley, adult	0.6% Pb acetate in drinking water; ad libitum for various durations as follows: GD 5 to PND 1, GD 5 to weaning, PND 1 to weaning	Female pups exposed to Pb from birth through adulthood or from GD 5 through adulthood were observed to have significantly delayed vaginal opening and disrupted estrus cycling; these effects on female reproductive physiology were not observed in animals where Pb exposure was confined only to pregnancy or lactation.	Pups continuously exposed to Pb 225 to 325 µg/dL
Ronis et al. (1998b)	Rat/Sprague-Dawley, adult	Ad libitum intake of Pb acetate (0.05 to 0.45% w/v); Pb exposure of dams until weaning, exposure of pups until day 21, 35, 55, 85	Prenatal Pb exposure that continues until adulthood (85 days old) delays sexual maturation in female pups in a dose-related manner; dose-dependent delay in sexual maturation (delayed vaginal opening) among female rats following prenatal Pb exposure that continued until adulthood (85 days old); a growth hormone-mediated effect on growth that differs depends upon the developmental state of the animal birth weight was significantly reduced and more pronounced among male pups; decreased growth rates in both sexes were accompanied by a statistically significant decrease in plasma concentrations of IGF1 through puberty and a significant increase in pituitary growth hormone during puberty; growth suppression of male and female rats involves disruption of growth hormone secretion during puberty.	Mean PbB in offspring at 0.05% (w/v) 49 ± 6 µg/dL Mean PbB in offspring at 0.15% (w/v) 126 ± 16 µg/dL Mean PbB in offspring at 0.45% (w/v) 263 ± 28 µg/dL
Ronis et al. (1998c)	Rat/Sprague Dawley, adult	0.05, 0.15, or 0.45% Pb acetate in drinking water beginning GD 5 for 21, 35, 55, 85 days	Dose-responsive decrease in birth weight and crown-to-rump length was observed in litters; dose-dependent delay in sexual maturity (delay in vaginal opening); decrease in neonatal sex steroid levels and suppression of E2 during puberty; elevation in pituitary LH content was observed during early puberty; E2 cycle was significantly disrupted at the highest Pb dose; data suggests that the reproductive axis is particularly sensitive to Pb during specific developmental periods, resulting in delayed sexual maturation produced by sex steroid biosynthesis.	PbB in dams 181 ± 14 µg/dL PbB in pups ranged from 197 ±82 to 263 ± 38 µg/dL, increasing with age of pups
Sierra and Tiffany-Castiglioni (1992)	Guinea pig/NOS, adult	0, 5.5, or 11 mg/kg Pb acetate, oral dose from GD 22 until GD 52 or 62	Hypothalamic levels of SRIF; lower serum concentrations of progesterone at higher dose only; hypothalamic levels of GnRH and SRIF were reduced in a dose-dependent manner by Pb treatment in both dams and fetuses; reduction of SRIF levels in 52-days old fetus was particularly severe (92%) in the 11 mg group.	PbB not reported
Srivastava et al. (2004)	Rat/Fisher 344, adult	12 mg/mL Pb acetate by gavage for 30 days prior to breeding until weaning	Pb decreased StAR protein expression and lowered E2 levels; suggested that the primary action of Pb to suppress E2 is through its known action to suppress the	PbB of dams 39 ± 3.5 SEM µg/dL and offspring PbB 2.9

Table AX5-4.3. Effect of Lead on Reproduction and Development in Mammals Effects on Females

Citation	Species/ Strain/Age	Dose/Route/ Form/Duration	Endpoint	Blood Lead Concentration (PbB)
			serum levels of LH and not due to decreased responsiveness of StAR synthesizing machinery.	±0.28 SEM µg/dL
Taupeau et al. (2001)	Mouse/C57blxCBA, 8 wks old	10 mg/kg-d Pb nitrate via i.v. for 15 days	Low Pb concentration in the ovary caused dysfunction of folliculogenesis, with fewer primordial follicles and an increase in atretic antral follicles.	PbB not reported
Tchernitchin et al. (1998a)	Rat/Sprague Dawley, 14 days old	172 µg/g bw Pb from day 14 every 2nd day until day 20	Pb inhibits estrogen-induced uterine eosinophilia at 6 and 24 hr after treatment; Pb also inhibits estrogen-induced edema in deep and superficial endometrial stoma at 24 hr but not 6 hr after treatment; myometrial hypertrophy is inhibited under the effect of exposure at 24 hr of treatment.	PbB 47 µg/dL
Tchernitchin et al. (1998b)	Rat/Sprague Dawley, 20 or 21 days old	(75 mg/g bw) Pb via i.v. one time exposure at 1 or 24 before hormone stimulation	Enhanced some parameters of estrogen stimulation and inhibited other estrogenic responses; interaction with responses to estrogen was different depending on whether Pb pretreatment was 1 or 24 hr before hormone stimulation; estrogenic responses mostly affected were uterine eosinophilia, endometrial edema, uterine liminal epithelial, hypertrophy, and mitosis in various, but not all, uterine cell types, in some cell types, estrogen-induced mitotic response developed earlier under the effect of Pb exposure.	PbB not reported
Wide (1985)	Mouse/NMRI, 10 wks old	20 µg/dL/g bw Pb chloride via i.v. single exposure on days 8, 12, or 16 after mating	Litter size and fetal survival varied significantly; small litters and increased numbers of fetal deaths were observed in mice exposed to Pb on day 8 of intrauterine life; live fetuses were normal with respect to weight and morphological appearance; ovarian follicle counts revealed a significantly smaller number of primordial follicles in the latter group, it suggested that the exposure to Pb at a time of early organogenesis caused the observed fertility decrease by interfering with the development of the female germ cells.	PbB not reported
Wide and D'Argy (1986)	Mouse/NMRI, adult	20 µg/g bw by i.v. single injection on GD 8	Primordial germ cells showed a normal body distribution but were significantly fewer at all four stages compared with those of control embryos of corresponding age; Pb had interfered with the production or activity of alkaline phosphatase.	PbB not reported
Wiebe and Barr (1988)	Rat/Sprague Dawley, adult	20 or 200 ppm Pb chloride in drinking water; 3 exposure durations; prior to mating through weaning, GD 7 to weaning, PND 21 to PND 35	Treatment with Pb prior to mating resulted in significant increase in E2-receptor affinity in 21-day old offspring without a change in E2 receptor number; treatment from day 7 of pregnancy until weaning of the pups resulted in ~35% decrease in E2 receptors per mg uterine protein when these offspring reached 150 days of age; Pb treatment from 21–35 days old or until 150 days resulted in a significant decrease in uterine E2 receptor number at 35 and 150 day, respectively.	PbB likely 4.0 ± 1.4 to 6.6 ± 2.3 µg/dL (similar design as Wiebe et al. (1988)
Wiebe et al. (1988)	Rat/Sprague Dawley, adult	20 or 200 ppm Pb chloride in drinking water; 4 exposure durations; prior to mating through weaning, GD 7 to weaning, PND 21 to PND 35, prior to mating only	Exposure to Pb did not affect tissue weights but did cause a significant decrease in gonadotropin-receptor binding in the pre-pubertal, pubertal, and adult females; conversion of progesterone to androstenedione and dihydrotestosterone was significantly decreased in 21-day old rats and in 150-day old females; significantly increased conversion to the 5-alpha-reduced steroids, normally high during puberty.	PbB range 4.0 ± 1.4 to 6.6 ± 2.3 µg/dL
Yu et al. (1996)	Rat/Sprague-Dawley, adult	Neonatal and lactational exposure to 0.3% Pb acetate in drinking water (PND 30)	Neonatal exposure to Pb decreased cold-water swimming endurance (a standard test for stress endurance); delayed onset of puberty in males and female offspring, which was exacerbated by swimming stress.	PbB 70 µg/dL

*Not including effects on the nervous or immune systems.

† Candidate key study.

E2, estradiol; FSH, follicle stimulating hormone; GD, gestational day; GnRH, gonadotropin releasing hormone; HET, Binghamton Heterogeneous Stock; IGF1, insulin-like growth factor 1; i.p., intraperitoneal; LH, luteinizing hormone; NOS, not otherwise specified; PbB, blood lead concentration; PND, post-natal day; p.o., per os (oral administration); SRIF, somatostatin; StAR, steroidogenic acute regulatory protein.

Appendix E. Updated Literature on the Developmental and Reproductive Effects of Lead in Humans

(January 31, 2007 – October 16, 2007)

Appendix E. Literature on the Reproductive and Developmental Effects of Lead in Human (January 31, 2007 – October 16, 2007)*

Reference and Study Location	Study Description	Pb Measurement	Findings, Interpretation
United States			
Adams et al. (2007) U.S.	This study determined the level of mercury, lead, and zinc in baby teeth of children with autism spectrum disorder (n = 15, age 6.1 +/- 2.2 yr) and typically developing children (n = 11, age = 7 +/- 1.7 yr).	Baby teeth Pb	Higher levels of mercury, but similar levels of Pb and zinc in typically developing children and children with autism spectrum disorder
Braun et al. (2006) U.S.	Cross-sectional study that examined the association of exposures to tobacco smoke and environmental Pb with attention deficit hyperactivity disorder (ADHD). Prenatal and postnatal tobacco exposure was based on parent report; Pb exposure was measured using blood Pb concentration. ADHD was defined as having current stimulant medication use and parent report of ADHD diagnosed by a doctor or health professional.	Blood Pb	In multivariable analysis, prenatal tobacco exposure [odds ratio (OR) = 2.5; 95% confidence interval (CI), 1.2-5.2] and higher blood lead concentration (first vs. fifth quintile, OR = 4.1; 95% CI, 1.2-14.0) were significantly associated with ADHD. Postnatal tobacco smoke exposure was not associated with ADHD (OR = 0.6; 95% CI, 0.3-1.3; p = 0.22). Authors conclude that exposure to prenatal tobacco and environmental lead are risk factors for ADHD in U.S. children and that, if causally linked, Pb may contribute for 290,000 excess cases of ADHD in U.S. children
Chen et al. (2007) U.S.	Prospective observational study to differentiate the direct effect of Pb on behavior and the indirect effect through IQ and to examine the strength of the association for peak and concurrent blood Pb concentration. Data come from a clinical trial of the chelating drug succimer to prevent cognitive impairment in 780 urban 12- to 33-month-olds with blood Pb of 20 to 44 microg/dL.	Blood Pb	Blood Pb at 2 yrs old was not associated with Conners' Parent Rating Scale-Revised scores at 5 yrs of age or Behavioral Assessment Systems for Children scores at 7 yrs of age. Blood Pb at 7 yrs of age had direct effects on the Behavioral Assessment Systems for Children behavioral symptoms index, externalizing, and school problems at age 7. Authors conclude that concurrent blood Pb was associated with externalizing and school problems scales at 7 years of age, and the effect was not entirely mediated through the effect of lead on IQ.
Froehlich et al. (2007) U.S.	Multivariable analyses were used to examine effects of DRD4-7 genotype, 60-month blood Pb level, and sex on spatial working memory, rule learning and reversal, spatial span, and planning for 174 children.	Blood Pb	DRD4-7 was associated with poorer spatial working memory, and increasing blood Pb levels were associated with impaired rule learning and reversal, spatial span, and planning. Effects of Pb on planning and rule learning and reversal were seen primarily for boys. The effect of Pb on rule learning and reversal was evident predominately for those lacking DRD4-7. Authors conclude that DRD4-7 and Pb have independent effects on various executive functions and modifications of Pb effects by DRD4 genotype and sex.
Gump et al. (2007) U.S.	The role of Pb in mediating the reported association between socioeconomic status (SES) and total peripheral (vascular) resistance (TPR) was investigated in 122 9.5-year-old children with established early childhood blood lead levels. Family SES was measured using the Hollingshead Index, blood Pb levels were	Blood Pb	Lower family SES was shown to be associated with significantly higher blood Pb levels as well as significantly heightened systolic blood pressure, diastolic blood pressure, and TPR responses to acute stress tasks. A mediational analysis confirmed that Pb was a significant mediator of the SES-TPR reactivity association; some evidence also suggested moderation.

Appendix E. Literature on the Reproductive and Developmental Effects of Lead in Human (January 31, 2007 – October 16, 2007)*

Reference and Study Location	Study Description	Pb Measurement	Findings, Interpretation
	abstracted from pediatrician and state records, and children's cardiovascular responses to acute stressors were measured in the laboratory with impedance cardiography and an automated blood pressure monitor.		
Hu et al. (2006) Mexico	Prospective longitudinal study to study the impact of prenatal Pb on neurodevelopment using repeated measures of fetal and infant dose as reflected by Pb in maternal whole blood, maternal plasma, umbilical cord blood at delivery, and in offspring at 12 and 24 months of age (n=146). .Mental development was assessed using Bayley Scales of Infant Development.	Blood and plasma Pb 1st trimester maternal lead levels: 7.1 +/- 5.1 μg/dL (14% ≥ 10 μg/dL)	Both maternal plasma and whole blood Pb during the first trimester (but not in the second or third trimester) were significant predictors of poorer Mental Development Index (MDI) scores. A 1-standard deviation change in first-trimester plasma Pb was associated with a reduction in MDI score of 3.5 points. Postnatal blood Pb levels in the offspring were less strongly correlated with MDI scores. Authors conclude that fetal Pb exposure has an adverse effect on neurodevelopment, with an effect that may be most pronounced during the first trimester and best captured by measuring Pb in either maternal plasma or whole blood.
Hubbs-Tait et al. (2007) U.S.	A cross-sectional and correlational study to conduct a preliminary investigation of lead, zinc, and iron levels in relation to child cognition and behavior in a small sample of Head Start children (42 children 3- to 5-yrs of age). Children's behavior assessed by the California Preschool Social Competency Scale, Howes' Sociability subscale, Preschool Behavior Questionnaire, and McCarthy Scales of Children's Abilities.	Blood Pb	Pb levels explained 25% of the variance in teacher ratings of girls' sociability and 20% of the variance in teacher ratings of girls' classroom competence. The four children low in zinc and iron had significantly higher blood Pb than the 31 children sufficient in zinc or iron or the 7 children sufficient in both. The authors conclude that iron, zinc, and lead have both separate and interacting effects in this study population
Huo et al. (2007) China	Comparison of blood Pb, hemoglobin (Hgb) and physical indexes (height and weight, head and chest circumferences) in 226 children < 6 years of age living in a town with primitive electronic waste recycling (Guiye, n=165) or a neighboring town (Chendian, n = 61).	Blood Pb Guiyu BLL: 4.40 to 32.67 μg/dL; mean=15.3 μg/dL Chendian BLL: 4.09 to 23.10 μg/dL;mean=9.94 μg/dL.	Of children in Guiyu, 81.8% had BLLs > 10 μg/dL, compared with 37.7% of Chendian children. No significant difference in Hgb level or physical indexes was found between the two towns.
Ignasiak et al. (2007) Poland	A study to investigate whether Pb has a direct effect on measures of physical fitness and, if so, whether this is an indirect effect mediated through growth stunting. Blood Pb was tested in schoolchildren 7-15 years of age (463 males, 436 females) living in the vicinity of copper smelters and refineries. In addition to body size	Blood Pb	The effect of blood lead level on physical fitness was indirect and small, and operated through anthropometric dimensions that more directly influenced the measures of fitness. Authors conclude that blood Pb adversely affects physical fitness indirectly through growth stunting.

Appendix E. Literature on the Reproductive and Developmental Effects of Lead in Human (January 31, 2007 – October 16, 2007)*

Reference and Study Location	Study Description	Pb Measurement	Findings, Interpretation
	and blood lead, simple reaction time and physical fitness was measured: right and left grip strength, timed sit-ups, flexed arm hang, plate tapping, shuttle run, standing long jump and medicine ball throw.		
Iranpour et al. (2007) Iran	A cross-sectional prospective study comparing the blood Pb levels of mothers and cord blood in 32 mother-infant pairs with full term intrauterine growth retarded (IUGR) neonates and 34 mother-infant pairs with normal term neonates. Blood lead levels were measured in the umbilical cord and maternal venous blood samples in neonates, and with normal full term neonates.	Blood Pb	Average Pb level was not higher in IUGR neonates and whole blood Pb level was not related to the birth weight.
Kern et al. (2007) U.S.	Cross-sectional study to examine differences in sulfhydryl-reactive metals (mercury, lead, arsenic, and cadmium) in the hair of 45 children with autism (1-6 yr of age) as compared to 45 gender-, age-, and race-matched typical children.	Hair Pb	Pb, arsenic, and cadmium were significantly lower in the hair of children with autism than in matched controls. Authors conclude that this study supports the notion that children with autism may have trouble excreting these metals, resulting in a higher body burden that may contribute to symptoms of autism.
Martin et al. (2007) U.S.	This cross-sectional study examined the relationship of Pb exposure and dental caries in a population of 507 healthy children aged 8-12 who were participating in a clinical trial of dental materials. Blood Pb concentrations and dental caries were examined for association in both primary and permanent teeth. Neurobehavioral status of the children was also assessed because it could be associated with both lead exposure and dental caries prevalence.	Blood Pb	A gender-specific association (males only) between lead exposure and dental caries was found in primary teeth only. Neurobehavioral measures and IQ were not associated with caries status in this population. Authors conclude that this study provides only weak evidence, if any, for an association of low-level lead exposure with dental caries.
Min et al. (2007)	This study assessed the association between neurodevelopmental performance and Pb exposure below 5 microg/dl in 61 Korean children aged 7-16 yrs. Neurodevelopmental function was measured with computer-based neurobehavioral tests.	Blood Pb	For simple reaction time and digit span, which, respectively reflect attention and short-term memory, there was a small and significant association between the children's neurodevelopmental performance and their blood lead levels (p=0.05, 0.08, respectively). Authors conclude the study suggests that low blood lead below 5 microg/dl can influence children's neurobehavioral performance.
Miranda et al. (2007) U.S.	Population-level analysis to determine whether blood Pb levels in early childhood are related to	Blood Pb	The impact of blood lead levels on EOG testing is demonstrated for early childhood blood Pb levels as low as 2 microg/dL. A blood lead level of 5 microg/dL is associated

Appendix E. Literature on the Reproductive and Developmental Effects of Lead in Human (January 31, 2007 – October 16, 2007)*

Reference and Study Location	Study Description	Pb Measurement	Findings, Interpretation
	educational achievement in early elementary school as measured by performance on end-of-grade (EOG) testing. Educational testing data for +35,000 4th-grade students from the 2000-2004 North Carolina Education Research Data Center were linked to blood lead surveillance data for seven counties in North Carolina.		with a decline in EOG reading (and mathematics) scores that is roughly equal to 15% (14%) of the interquartile range. Early childhood lead exposures appear to have more impact on performance on the reading than on the mathematics portions of the tests.
Nevin (2007)	This study assessed the relationship between preschool Pb and subsequent crime rate trends over several decades in the USA, Britain, Canada, France, Australia, Finland, Italy, West Germany, and New Zealand. Pb blood data was based on estimated preschool blood Pb trend estimates, anchored to surveillance data like that provided in the U.S. by the National Health and Nutrition Examination Survey (NHANES). Index crimes include threats, property crimes (burglary and theft) and the violent crimes of murder, rape, robbery, and aggravated assault (causing injury or with a lethal weapon), simple assaults without injury, and petty thefts below a USA monetary threshold for larceny.	Blood Pb	The authors report a very strong association between preschool blood Pb and subsequent crime rate trends over several decades in the USA, Britain, Canada, France, Australia, Finland, Italy, West Germany, and New Zealand as characterized by best-fit lags (highest R2 and t-value for blood lead) consistent with neurobehavioral damage in the first year of life and the peak age of offending for index crime, burglary, and violent crime. The impact of blood lead is also evident in age-specific arrest and incarceration trends.

*Studies identified by a PubMed search using lead, the CAS RN for lead (7439-92-1), and "lead" as a text term to identify various salts. The search covered the period of January 31, 2007 to October 16, 2007. Two additional relevant studies published in 2006 (and not reviewed in the EPA Air Quality Criteria for Lead document) were identified by 2007 author's correspondence and included.

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Hubbs-Tait, L., T. S. Kennedy, et al. (2007). "Zinc, iron, and lead: relations to head start children's cognitive scores and teachers' ratings of behavior." J Am Diet Assoc **107**(1): 128-33.

Huo, X., L. Peng, et al. (2007). "Elevated blood lead levels of children in Guiyu, an electronic waste recycling town in China." Environ Health Perspect **115**(7): 1113-7.

Ignasiak, Z., T. Slawinska, et al. (2007). "Blood lead level and physical fitness of schoolchildren in the copper basin of south-western Poland: indirect effects through growth stunting." Ann Hum Biol **34**(3): 329-43.

Iranpour, R., A. A. Besharati, et al. (2007). "Comparison of blood lead levels of mothers and cord blood in intrauterine growth retarded neonates and normal term neonates." Saudi Med J **28**(6): 877-80.

Kern, J. K., B. D. Grannemann, et al. (2007). "Sulfhydryl-reactive metals in autism." J Toxicol Environ Health A **70**(8): 715-21.

Martin, M. D., T. Benton, et al. (2007). "The association of dental caries with blood lead in children when adjusted for IQ and neurobehavioral performance." Sci Total Environ **377**(2-3): 159-64.

Min, J. Y., K. B. Min, et al. (2007). "Neurobehavioral function in children with low blood lead concentrations." Neurotoxicology **28**(2): 421-5.

Miranda, M. L., D. Kim, et al. (2007). "The relationship between early childhood blood lead levels and performance on end-of-grade tests." Environ Health Perspect **115**(8): 1242-7.

Nevin, R. (2007). "Understanding international crime trends: the legacy of preschool lead exposure." Environ Res **104**(3): 315-36.

Appendix F. Updated Literature on the Developmental and Reproductive Effects of Lead in Experimental Animals and *In Vitro* Models

(January 31, 2007 – October 16, 2007)

Bakheet, S. A., M. R. Basha, et al. (2007). "Lead exposure: expression and activity levels of Oct-2 in the developing rat brain." Toxicol Sci 95(2): 436-42.

Lead is a highly neurotoxic metal, and the developing central nervous system is particularly vulnerable to the effects of lead. In this study, transcription factors (TFs) that are altered due to lead exposure were identified using macroarray analysis. Rat pups were lactationally exposed to 0.2% lead acetate from birth through weaning. Changes in the developmental profiles of 30 TFs were screened in hippocampal tissue on postnatal day (PND) 5, 15, and 30. The temporal patterns of some TFs were transiently upregulated or repressed following lead exposure in a stage-specific manner; however, Oct-2, which is involved in the regulation of key developmental processes, exhibited sustained elevations during the entire period of study. Lead-induced elevation of Oct-2 was validated by reverse transcriptase-polymerase chain reaction analysis; however, significant elevation of Oct-2 mRNA expression was detected only on PND 5. The DNA-binding activity and protein levels of Oct-2 were further evaluated and found to be consistently induced on PND 5. The elevations observed in Oct-2 mRNA and protein levels as well as DNA-binding activity on PND 5 suggest that developmental maintenance of Oct-2 DNA binding could be impacted through de novo synthesis. These findings identify Oct-2 as a potential molecular target for Pb and suggest that Oct-2 may be associated with lead-induced disturbances in gene expression.

Beaudin, S. A., D. E. Stangle, et al. (2007). "Succimer chelation normalizes reactivity to reward omission and errors in lead-exposed rats." Neurotoxicol Teratol 29(2): 188-202.

This study evaluated the efficacy of a 3-week course of succimer treatment to alleviate behavioral deficits in rats exposed to lead (Pb) for the first 4 weeks of life. A 3 x 2 factorial design was used: three levels of lead exposure (No Pb, Moderate, and High Pb) and two levels of chelation (succimer or vehicle). Behavioral testing was conducted following chelation therapy, from 2 to 9 months of age; this report presents the results of two of the administered tasks: (1) a conditional olfactory discrimination task (baseline task), and (2) a conditional olfactory discrimination task with periodic reward omission on some correct trials (RO task). In the RO task, the performance disruption produced by committing an error on the previous trial was significantly greater for both unchelated lead-exposed groups than for controls. The High Pb rats were also more sensitive to reward omission than controls, providing converging evidence for impaired regulation of arousal or emotion. Importantly, succimer treatment was effective in normalizing the heightened reactivity of the lead-exposed animals to both errors and reward omission. In addition, non-lead-exposed rats that were treated with succimer tended to be more affected by a prior error than controls in their latency to respond on post-error trials. In sum, these findings provide new evidence that succimer chelation can significantly lessen the lasting neurobehavioral dysfunction produced by early lead exposure, but also suggest that there may be risks of administering the drug to individuals without elevated blood lead levels.

Chetty, C. S., M. C. Vemuri, et al. (2007). "Protective effect of 17-beta-estradiol in human neurocellular models of lead exposure." Neurotoxicology 28(2): 396-401.

The developing nervous system has long been recognized as a primary target site for lead (Pb)-induced toxicity. Pb-exposure causes cognitive dysfunction, growth retardation, hyperactivity and neurochemical deficits in animals and humans. In the present study the effects of 17-beta-estradiol on human SH-SY5Y neuroblastoma cells in culture exposed to low-levels of Pb were assessed. The cells were exposed to Pb (0.01-10 microM) for 48 h and cell proliferation was determined by the MTT reduction assay. Pb significantly inhibited the proliferation and growth of neuroblastoma cells in a concentration-dependent manner. A 50% inhibition (IC50) in the proliferation of cells was observed with 5 microM Pb. Exposure of cells to Pb (5 microM) for 48

h resulted in a significant increase (+732% of control) in caspase-3 activity, an indicator of apoptosis and total cellular prostaglandin E2 level (+1180% of control), marker of programmed cell death/neuronal cell loss. Pretreatment with 17-beta-estradiol (10 nM) effectively blocked the effects of Pb on caspase-3 activity but not prostaglandin E2 level. Further, Pb but not 17-beta-estradiol in a concentration (0.1-10 microM)-dependent manner effectively decreased (38-84%) the cellular concentration of glutathione (GSH), an important intracellular antioxidant. However, the effect of Pb on GSH level was effectively blocked when pretreated with 17-beta-estradiol. The data indicate that even low concentrations of Pb can be detrimental and potentially toxic to the developing brain. In conclusion, these results suggest that at least some of the neurotoxic effects of Pb may be mediated by apoptosis, which by pretreatment with 17-beta-estradiol can be prevented. This study further confirms previous reports of 17-beta-estradiol acting as a neuroprotective and antiapoptotic agent during induced toxic stress conditions.

Gilbert, M. E. and S. M. Lasley (2007). "Developmental lead (Pb) exposure reduces the ability of the NMDA antagonist MK-801 to suppress long-term potentiation (LTP) in the rat dentate gyrus, in vivo." Neurotoxicol Teratol 29(3): 385-93.

Chronic developmental lead (Pb) exposure increases the threshold and enhances decay of long-term potentiation (LTP) in the dentate gyrus of the hippocampal formation. MK-801 and other antagonists of the N-methyl-D-aspartate (NMDA) glutamate receptor subtype impair induction of LTP. In addition, Pb exposure reduces presynaptic glutamate release and is associated with alterations in NMDA receptor expression. This study examined LTP in Pb-exposed animals challenged with a low dose of MK-801 to assess the sensitivity of this receptor to inhibition. Pregnant rats received 0.2% Pb acetate in the drinking water beginning on gestational day 16, and this regimen was continued through lactation. Adult male offspring maintained on this solution from weaning were prepared with indwelling electrodes in the perforant path and dentate gyrus. Several weeks later, input/output (I/O) functions were collected in awake animals before and after saline or MK-801 administration (0.05 mg/kg, s.c.). LTP was induced using suprathreshold train stimuli 60 min post-drug. Post-train I/O functions were reassessed 1 and 24 h after train delivery. Upon full decay of any induced LTP, drug conditions were reversed such that each animal was tested under saline and MK-801. I/O functions measured 1 and 24 h after train induction as well as immediate post-train responses revealed significant LTP of comparable magnitude that was induced in both control and Pb-exposed animals tested under saline conditions. In contrast, MK-801 reduced LTP in control but not in Pb-exposed animals. The broadening of the excitatory postsynaptic potential evident in responses evoked by train stimuli is NMDA-dependent. Pb exposure attenuated the MK-801-induced reduction in area of this NMDA component by approximately 50%. These findings are consistent with other neurochemical and behavioural observations and suggest that up-regulation of postsynaptic NMDA receptors produces subsensitivity to the inhibitory effects of MK-801 on hippocampal LTP following chronic developmental Pb exposure.

Jamieson, J. A., J. N. Shuhyta, et al. (2007). "Lead does not affect transcription of intestinal zinc-binding proteins in growing rats." Exp Biol Med (Maywood) 232(6): 744-53.

Environmental lead exposure remains a serious concern for the growth and development of children. Micronutrient status may affect the absorption and tissue accumulation of lead, but the mechanisms of gastrointestinal uptake and transport remain unknown. Thus, our objective was to investigate the effects of lead on the mRNA levels of intestinal zinc transporter 4 (ZIP4), metallothionein (MT), cysteine-rich intestinal protein (CRIP), and divalent metal transporter 1 (DMT1) in growing rats fed marginal, adequate, and supplemental zinc diets. Weanling Sprague

Dawley rats were assigned to marginal zinc (MZ; 8 mg Zn/kg diet), zinc-adequate control (CT; 30 mg Zn/kg), zinc-adequate diet-restricted (DR; 30 mg Zn/kg), or supplemental zinc (SZ; 300 mg Zn/kg) groups, with and without lead acetate-containing drinking water (200 mg Pb/l) for 3 weeks. Duodenum was analyzed for ZIP4, MT, CRIP, and DMT1 mRNA levels by real-time reverse transcription-polymerase chain reaction and MT immunolocalization. Tissues were analyzed for zinc, lead, and iron by inductively coupled plasma spectrometry. MZ rats had higher duodenal ZIP4 mRNA levels, lower MT mRNA levels, lower MT immunostaining intensity, and lower zinc concentrations than DR, CT, and SZ. Duodenal DMT1 mRNA levels were lower in DR and SZ compared with MZ. Tissue lead concentrations responded to dietary zinc with SZ < CT < DR <or= MZ. The greater accumulation of hepatic lead in MZ rats was associated with zinc deficiency as well as diet restriction. Lead treatment resulted in higher hepatic iron concentrations but had no effect on duodenal ZIP4, MT, CRIP, or DMT1 mRNA levels. Thus, tissue lead accumulation was not directly mediated by the transcriptional induction of zinc and iron binding or transport proteins. The mechanisms of lead absorption during nutritional deficiency and supplementation require further investigation.

Karaca, T. and N. Simsek (2007). "Effects of spirulina on the number of ovary mast cells in lead-induced toxicity in rats." Phytother Res 21(1): 44-6.

The present study investigated the protective effect of Spirulina against the lead-induced increase in mast cells in the ovary during the oestrous cycle of rats. In the ovary cortex and medulla of lead-exposed animals, there was a significant increase in the number of mast cells; however, when also treated with Spirulina, a decrease was observed. The number of mast cells when Spirulina (300 mg/kg) was used alone was not significantly different from that of the control group. These results indicate that Spirulina decreases the number of mast cells induced by lead in the cortex and medulla of rat ovary.

Marchlewicz, M., B. Wiszniewska, et al. (2007). "Increased lipid peroxidation and ascorbic Acid utilization in testis and epididymis of rats chronically exposed to lead." Biometals 20(1): 13-9.

The hypothesis has been recently presented that lead may exert its negative effect at least partially through the increase of reactive oxygen species (ROS) level in tissues. However, little is known about the influence of lead intoxication on equilibrium between generation and elimination of ROS in the male reproductive system. Sexually mature male Wistar rats were given ad libitum 1% of aqueous solution of lead acetate (PbAc) for 9 months. Significantly higher lead concentrations were found in blood [median 7.03 (Q25-Q75: 2.99-7.65) versus 0.18 (0.12-0.99) microg dl-1, $P < 0.01$], caput epididymis [median 5.51 (Q25-Q75: 4.31-7.83) versus 0.51 (0.11-0.80) microg g-1 d.m., $P < 0.001$], cauda epididymis [median 5.88 (Q25-Q75: 4.06-8.37) versus 0.61 (0.2 - 1.08) microg g-1 d.m., $P < 0.001$] and testis [median 1.81 (Q25-Q75: 0.94-2.31) versus 0.17 (0.03-0.3) microg g-1 d.m., $P < 0.01$] of lead-intoxicated rats when compared to the control. The concentration of ascorbyl radical, generated in vitro from L: -ascorbic acid (present in tissues in vivo) was measured by means of Electron Paramagnetic Resonance (EPR) spectroscopy. The EPR signal of ascorbyl radical in caput epididymis, cauda epididymis, testis and liver of lead acetate-treated animals revealed a significant decrease by 53%, 45%, 40% and 69% versus control tissues, respectively. Plasma L: -ascorbic acid content measured by high performance liquid chromatography (HPLC) method and total antioxidant status (TAS) measured by means of spectrophotometry were also significantly lower in the intoxicated versus control animals (28% and 21%, respectively). In the group exposed to lead the concentration of lipid peroxide in homogenates of the reproductive system organs was significantly elevated versus control group. It can be assumed that the lower EPR signal was caused by decreased tissue

concentrations of L: -ascorbic acid. The latter may have resulted from consumption of ascorbic acid for scavenging of ROS excess in tissues of animals chronically exposed to lead.

Massanyi, P., N. Lukac, et al. (2007). "Lead-induced alterations in rat kidneys and testes in vivo." J Environ Sci Health A Tox Hazard Subst Environ Eng 42(5): 671-6.

The purpose of this study was to assess the effects of lead administration on the kidney and testicular structure of adult rats. Rats received lead (PbNO(3)) in single intraperitoneal dose 50 mg/kg (group A), 25 mg/kg (group B) and 12.5 mg (group C) per kilogram of body weight and were killed 48 h following lead administration. After the preparation of histological samples the results were compared with control. After the lead administration dilated Bowman's capsules and blood vessels in interstitium of kidney with evident hemorrhagic alterations were noted. Quantitative analysis determined increased relative volume of interstitium and tubules. Also, the diameter of renal corpuscules, diameter of glomeruli and diameter of Bowman's capsule were significantly increased, especially in group A, with the highest lead concentration. In testes, dilatation of blood capillaries in interstitium, undulation of basal membrane and occurrence of empty spaces in seminiferous epithelium were detected. An apoptosis assay confirmed increased incidence of apoptosis in the spermatogenetic cells after the lead administration. Also further morphometric analysis showed significant differences in evaluated parameters between control and treated groups. The number of cell nuclei was decreased in lead-treated groups, which is concerned with the occurrence of empty spaces as well as with the higher apoptosis incidence in germinal epithelium. This study reports a negative effect of lead on the structure and function of kidney and testes.

Nampoothiri, L. P., A. Agarwal, et al. (2007). "Effect of co-exposure to lead and cadmium on antioxidant status in rat ovarian granulose cells." Arch Toxicol 81(3): 145-50.

The effects of combined exposure to lead and cadmium on granulose cells were studied. Adult female rats were treated i.p. with either lead acetate (LA) or cadmium acetate (CA) both, alone, or in combination at a dose of 0.05 mg/kg body weight on a daily basis for 15 days. Both metals were accumulated in the ovary after metal exposure. Metal exposure caused a decrease in reduced glutathione content along with elevated lipid peroxidation in all groups. Granulose cells of both cadmium as well as combination group demonstrated a maximum increase in lipid peroxides and catalase activity, along with decreased glutathione status and superoxide dismutase activities. Combined treated animals exhibited an intermediate effect in antioxidant status. However, "in vitro" exposure showed no significant change in antioxidant enzymes in all metal exposed cells. Data from the present study indicates that lead and cadmium in isolation and in combination cause oxidative stress. Lead and cadmium in combination do not show additive or synergistic effect indicating the competition between them due to similarity in electronic affinities. Present study highlights the effects of toxic metals that disturb membrane integrity of cells via ROS and thereby classifying mechanism for altered receptor binding, steroidogenesis, and hormone production.

Reddy, G. R., B. C. Devi, et al. (2007). "Developmental lead neurotoxicity: alterations in brain cholinergic system." Neurotoxicology 28(2): 402-7.

Developing brain has been shown to be susceptible to the neurotoxic effects of lead (Pb). Our earlier studies (Reddy GR, Riyaz Basha Md, Devi CB, Suresh A, Baker JL, Shafeek A, Heinz J, Chetty CS. Lead induced effects on acetylcholinesterase activity in cerebellum and hippocampus of developing rat. Int J Devl Neurosci 2003;21:347-52) have shown decrease in

acetylcholinesterase (AChE) activity in the crude homogenates of cerebellum and hippocampus of rat brain exposed to Pb. In this study, we have further examined in detail, the alterations in AChE activity and acetylcholine (ACh) levels in different brain regions using histochemical and spectrophotometric methods. Rats were lactationally exposed to low level (0.2%) and high level (1%) Pb. The studies were conducted in young (1 month) and adult (3 months) rats. Pb exposure significantly decreased the specific activity of AChE and increased the levels of ACh in the synaptosomal fractions of cerebellum, hippocampus and cerebral cortex in a dose- and age-dependent manner. These alterations in AChE and ACh were more predominant in young rat brain as compared to adult brain. Maximum AChE activity and ACh level as well as maximum alterations following Pb exposure were observed in synaptosomes of hippocampus. Histochemical studies also showed higher AChE activity in the hippocampal region compared to other areas of brain as revealed by the intensity of AChE staining. Though high level Pb exposure remarkably decreased the intensity of AChE staining in the dentate gyrus, CA2 and CA3 areas of hippocampus, and different cell layers of cortex and cerebellum, highly significant loss of AChE activity was observed in the CA3 region of hippocampus, molecular layer of cerebellum and cortical cell layers. These data suggest that Pb exposure may selectively affect cholinergic system in brain areas controlling learning and cognitive behavior.

Ryzhavskii, B., O. A. Lebed'ko, et al. (2007). "[Remote consequences of prenatal exposure to lead on the brain development in rats]." Morfologiia 131(1): 27-31.

Administration of a single dose of lead nitrate (200 mg/kg) to pregnant rats (Day 18 of gestation) resulted in the appearance of destructive brain changes in their offspring on postnatal Day 40, including the cysts, foci of glial cell proliferation, pyknosis of neurons, decrease of NADH- and NADPH-diaphorase activity in neocortical and hippocampal neurons. The reduction of both neuronal density in the cortex and cortical thickness was also demonstrated. The intensity of free radical oxidation in the cortex was increased 3-fold, while the concentration of lipid hydroperoxides was increased 3.9 times, and the resistance to peroxidation was decreased by a factor of 3, which is indicative of oxidative stress. Possible mechanisms of the pathological changes development are discussed.

Stangle, D. E., D. R. Smith, et al. (2007). "Succimer chelation improves learning, attention, and arousal regulation in lead-exposed rats but produces lasting cognitive impairment in the absence of lead exposure." Environ Health Perspect 115(2): 201-9.

BACKGROUND: There is growing pressure for clinicians to prescribe chelation therapy at only slightly elevated blood lead levels. However, very few studies have evaluated whether chelation improves cognitive outcomes in Pb-exposed children, or whether these agents have adverse effects that may affect brain development in the absence of Pb exposure. OBJECTIVES: The present study was designed to answer these questions, using a rodent model of early childhood Pb exposure and treatment with succimer, a widely used chelating agent for the treatment of Pb poisoning. RESULTS: Pb exposure produced lasting impairments in learning, attention, inhibitory control, and arousal regulation, paralleling the areas of dysfunction seen in Pb-exposed children. Succimer treatment of the Pb-exposed rats significantly improved learning, attention, and arousal regulation, although the efficacy of the treatment varied as a function of the Pb exposure level and the specific functional deficit. In contrast, succimer treatment of rats not previously exposed to Pb produced lasting and pervasive cognitive and affective dysfunction comparable in magnitude to that produced by the higher Pb exposure regimen. CONCLUSIONS: These are the first data, to our knowledge, to show that treatment with any chelating agent can alleviate cognitive deficits due to Pb exposure. These findings suggest that it may be possible to

identify a succimer treatment protocol that improves cognitive outcomes in Pb-exposed children. However, they also suggest that succimer treatment should be strongly discouraged for children who do not have elevated tissue levels of Pb or other heavy metals.

Struzynska, L., B. Dabrowska-Bouta, et al. (2007). "Inflammation-like glial response in lead-exposed immature rat brain." Toxicol Sci 95(1): 156-62.

Numerous studies on lead (Pb) neurotoxicity have indicated this metal to be a dangerous toxin, particularly during developmental stages of higher organisms. Astrocytes are responsible for sequestration of this metal in brain tissue. Activation of astroglia may often lead to loss of the buffering function and contribute to pathological processes. This phenomenon is accompanied by death of neuronal cells and may be connected with inflammatory events arising from the production of a wide range of cytokines and chemokines. The effects of prolonged exposure to Pb upon glial activation are examined in immature rats to investigate this potential proinflammatory effect. When analyzed at the protein level, glial activation is observed after Pb exposure, as reflected by the increased level of glial fibrillary acidic protein and S-100beta proteins in all parts of the brain examined. These changes are associated with elevation of proinflammatory cytokines. Production of interleukin (IL)-1beta and tumor necrosis factor-alpha is observed in hippocampus, and production of IL-6 is seen in forebrain. The expression of fractalkine is observed in both hippocampus and forebrain but inconsiderably in the cerebellum. In parallel with cytokine expression, signs of synaptic damage in hippocampus are seen after Pb exposure, as indicated by decreased levels of the axonal markers synapsin I and synaptophysin. Obtained results indicate chronic glial activation with coexisting inflammatory and neurodegenerative features as a new mechanism of Pb neurotoxicity in immature rat brain.

Svendsgaard, D., J. Y. Kim, et al. (2007). "A conclusion regarding: "what is the meaning of non-linear dose-response relationships between blood lead and IQ?"" Neurotoxicology 28(1): 196-7; author reply 197-201.

Swarup, D., R. Naresh, et al. (2007). "Changes in plasma hormones profile and liver function in cows naturally exposed to lead and cadmium around different industrial areas." Res Vet Sci 82(1): 16-21.

The present study was carried out to assess the endocrine status and liver function in adult cows reared in polluted environment around different industrial units in India.The effect on endocrine system was examined by determination of plasma level of thyroid hormones, thyroxin (T4) (n=269) and triidothyronin (T3) (n=269), stress hormone cortisol (n=266), and reproductive hormones such as estradiol (n=84) and progesterone (n=84) in cows (>3 years) reared around different polluted industrial and non-polluted areas.The respective blood lead and cadmium concentration was also determined in all the cows.The mean plasma levels of both T3 and T4 were significantly (P<0.05) higher around lead zinc smelter (2.43+/-0.26 and 41.1+/-2.9nmol/L) and closed lead cum operational zinc smelter (1.81+/-0.16 and 42.4+/-6.2nmol/L), where the mean blood lead level (0.86+/-0.06 and 0.51+/-0.09mug/ml) was also significantly higher than that of cows (0.07+/-0.01mug/ml) from unpolluted areas.Regression analysis of data from 269 cows revealed a significant (P<0.01) positive correlation between the blood lead and plasma T3 (r=0.287) and T4 (r=0.173).The correlation between thyroidal hormones and the blood cadmium concentration (r=-0.079 and -0.48; P>0.05) was not significant.Plasma cortisol level had also a non-significant (P>0.05) correlation (r=-0.092) with blood lead level.However, the mean cortisol level (4.02+/-1.96nmol/L) of cows in phosphate rock mining areas was significantly (P<0.05)

higher than that of controls (1.98+/-0.70nmol/L). The mean plasma estradiol level was significantly (P<0.05) higher in cows around closed lead cum operational zinc smelter (47.1+/-19.5pg/ml) than that of the control animals (21.8+/-3.9pg/ml) and in rest of the areas, the difference did not reach the statistical significance (P>0.05).The serum biochemical analysis in 36 cows around lead-zinc smelter with the highest mean blood lead level (0.86+/-0.06mug/ml) amongst all the industrial/urban areas surveyed, and in 15 animals from non-polluted areas revealed a significant positive correlation between blood lead and serum ALT (alanine transaminase) (r=0.688, P<0.01) and AST (aspartate transaminase) (r=0.390, P<0.01) and a negative correlation with serum total lipids (r=-0.337, P<0.05), total protein (r=-0.449, P<0.01) and albumin(r=-0.662, P<0.01). It is concluded from the study that the natural exposure to lead in polluted environments disturbs the endocrine profile and the higher blood lead level alters serum biochemical parameters indicative of liver functions.

Verina, T., C. A. Rohde, et al. (2007). "Environmental lead exposure during early life alters granule cell neurogenesis and morphology in the hippocampus of young adult rats." Neuroscience 145(3): 1037-47.

Exposure to environmentally relevant levels of lead (Pb(2+)) during early life produces deficits in hippocampal synaptic plasticity in the form of long-term potentiation (LTP) and spatial learning in young adult rats [Nihei MK, Desmond NL, McGlothan JL, Kuhlmann AC, Guilarte TR (2000) N-methyl-D-aspartate receptor subunit changes are associated with lead-induced deficits of long-term potentiation and spatial learning. Neuroscience 99:233-242; Guilarte TR, Toscano CD, McGlothan JL, Weaver SA (2003) Environmental enrichment reverses cognitive and molecular deficits induced by developmental lead exposure. Ann Neurol 53:50-56]. Other evidence suggests that the performance of rats in the Morris water maze spatial learning tasks is associated with the level of granule cell neurogenesis in the dentate gyrus (DG) [Drapeau E, Mayo W, Aurousseau C, Le Moal M, Piazza P-V, Abrous DN (2003) Spatial memory performance of aged rats in the water maze predicts level of hippocampal neurogenesis. Proc Natl Acad Sci U S A 100:14385-14390]. In this study, we examined whether continuous exposure to environmentally relevant levels of Pb(2+) during early life altered granule cell neurogenesis and morphology in the rat hippocampus. Control and Pb(2+)-exposed rats received bromodeoxyuridine (BrdU) injections (100 mg/kg; i.p.) for five consecutive days starting at postnatal day 45 and were killed either 1 day or 4 weeks after the last injection. The total number of newborn cells in the DG of Pb(2+)-exposed rats was significantly decreased (13%; P<0.001) 1 day after BrdU injections relative to controls. Further, the survival of newborn cells in Pb(2+)-exposed rats was significantly decreased by 22.7% (P<0.001) relative to control animals. Co-localization of BrdU with neuronal or astrocytic markers did not reveal a significant effect of Pb(2+) exposure on cellular fate. In Pb(2+)-exposed rats, immature granule cells immunolabeled with doublecortin (DCX) displayed aberrant dendritic morphology. That is, the overall length-density of the DCX-positive apical dendrites in the outer portion of the DG molecular layer was significantly reduced up to 36% in the suprapyramidal blade only. We also found that the area of Timm's-positive staining representative of the mossy fibers terminal fields in the CA3 stratum oriens (SO) was reduced by 26% in Pb(2+)-exposed rats. These findings demonstrate that exposure to environmentally relevant levels of Pb(2+) during early life alters granule cell neurogenesis and morphology in the rat hippocampus. They provide a cellular and morphological basis for the deficits in synaptic plasticity and spatial learning documented in Pb(2+)-exposed animals.

Wang, Q., W. Luo, et al. (2007). "Iron supplement prevents lead-induced disruption of the blood-brain barrier during rat development." Toxicol Appl Pharmacol 219(1): 33-41.

Children are known to be venerable to lead (Pb) toxicity. The blood-brain barrier (BBB) in immature brain is particularly vulnerable to Pb insults. This study was designed to test the hypothesis that Pb exposure damaged the integrity of the BBB in young animals and iron (Fe) supplement may prevent against Pb-induced BBB disruption. Male weanling Sprague-Dawley rats were divided into four groups. Three groups of rats were exposed to Pb in drinking water containing 342 microg Pb/mL as Pb acetate, among which two groups were concurrently administered by oral gavage once every other day with 7 mg Fe/kg and 14 mg Fe/kg as FeSO(4) solution as the low and high Fe treatment group, respectively, for 6 weeks. The control group received sodium acetate in drinking water. Pb exposure significantly increased Pb concentrations in blood by 6.6-folds ($p<0.05$) and brain tissues by 1.5-2.0-folds ($p<0.05$) as compared to controls. Under the electron microscope, Pb exposure in young animals caused an extensive extravascular staining of lanthanum nitrate in brain parenchyma, suggesting a leakage of cerebral vasculature. Western blot showed that Pb treatment led to 29-68% reduction ($p<0.05$) in the expression of occludin as compared to the controls. Fe supplement among Pb-exposed rats maintained the normal ultra-structure of the BBB and restored the expression of occludin to normal levels. Moreover, the low dose Fe supplement significantly reduced Pb levels in blood and brain tissues. These data suggest that Pb exposure disrupts the structure of the BBB in young animals. The increased BBB permeability may facilitate the accumulation of Pb. Fe supplement appears to protect the integrity of the BBB against Pb insults, a beneficial effect that may have significant clinical implications.

Xu, J., C. H. Yan, et al. (2007). "Developmental lead exposure alters gene expression of metabotropic glutamate receptors in rat hippocampal neurons." Neurosci Lett 413(3): 222-6.

Exposure to lead in utero and in infancy is associated with a risk of impaired cognitive development. Increasing evidence suggests that the family of metabotropic glutamate receptors (mGluRs) plays an important role in synaptic plasticity and memory formation. We determined whether mGluRs subtypes 1, 3, and 7 (mGluR1, mGluR3, and mGluR7) were involved in developmental neurotoxicity due to lead. Embryonic rat hippocampal neurons were cultured for 21 days and exposed to lead chloride beginning on the fourth day of incubation. We investigated levels of mGluR1, mGluR3, and mGluR7 mRNA expression by using quantitative real-time reverse-transcription polymerase chain reaction (RT-PCR) with lead exposure at 10 nM, 1 microM, and 100 microM. Lead exposure in vitro downregulated the expression of mGluR1 mRNA and upregulated the expression of mGluR3 and mGluR7 mRNA in a dose-dependent manner. We speculate that mGluRs may be involved in lead neurotoxicity. Pathways that likely contribute to lead neurotoxicity by means of mGluRs are impairment of long-term potentiation, effects on N-methyl-D-aspartate (NMDA) receptor functions, and depotentiation.

Yu, S. S., M. Wang, et al. (2007). "Influences of different developmental periods of taurine supplements on synaptic plasticity in hippocampal CA1 area of rats following prenatal and perinatal lead exposure." BMC Dev Biol 7: 51.

BACKGROUND: Previous study has demonstrated that dietary taurine supplement protected rats from impairments of synaptic plasticity induced by postnatal lead exposure. However, little is known about the role of taurine in the presence of prenatal and perinatal lead exposure. We investigated the possible effect of taurine supplement on prenatal and perinatal lead-induced synaptic plasticity deficit and determined developmental periods critical for the effect of taurine. RESULTS: In the present study, taurine was administrated to prenatal and perinatal lead-exposed rats in different developmental periods: from prenatal to weaning (Lead+PW-Tau), from weaning to life (Lead+WL-Tau), and from prenatal to life (Lead+PL-Tau). We examined the input-output

(I/O) function, paired-pulse facilitation (PPF) and the long-term potentiation (LTP) of field excitatory postsynaptic potential (fEPSP) in the hippocampal CA1 area of rats on postnatal days 18-25 (P18-25) or days 60-75 (P60-75). We found that (1) on P18-25, taurine had no evident effect on I/O functions and PPF ratios of lead-exposed rats but caused a 12.0% increase in the LTP amplitudes of these animals; (2) on P60-75, taurine significantly elevated lead depressed I/O functions and PPF ratios in Lead+PW-Tau and Lead+PL-Tau rats, but failed in Lead+WL-Tau rats. The amplitudes of LTP of lead-exposed rats were all significantly increased by additional taurine supplement in any developmental period compared with untreated rats. Thus, taurine appeared to have the most effect during the prenatal and lactation periods and its effects on younger rats would not be manifest until the adult life; and (3) the level of lead deposition in hippocampus was evidently reduced by additional treatment of taurine in lead-exposed rats, compared with untreated rats. CONCLUSION: Taurine supplement can protect the adult rats from synaptic plasticity deficits following prenatal and perinatal lead exposure, and the protective effects are critical for the prenatal and lactation periods of lead-exposed rats.